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Edited by

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Preface

Heterocyclic chemistry is of the utmost practical and theoretical importance. Heterocyclic compounds are in use as pharmaceuticals, dyes, pesticides, herbicides, plastics, and for many other purposes; the industries producing and researching into these products provide employment for a large fraction of all chemists. On the theoretical side, heterocyclic chemistry has provided a host of interesting concepts and structures. Yet, the subject is often deprived of the importance it deserves; it is said that it is possible to complete work at graduate schools of some universities without having attended a lecture course dealing specifically with heterocyclic chemistry.

I was indeed fortunate to have grown to chemical maturity under Sir Robert Robinson, and in an environment where heterocyclic chemistry was certainly not neglected. This being so, it is natural that I feel the dissemination and rationalization of knowledge in heterocyclic chemistry to be of vital importance. Recently several good heterocyclic texts have appeared, but a need exists for a medium in which current advances in the subject can rapidly be presented to a wide audience. The present series aims to make available to graduate students and research workers in academic and industrial laboratories up-to-date reviews of a wide variety of heterocyclic topics.

For this volume, and for succeeding volumes in the series, I have been fortunate in enlisting the cooperation of distinguished heterocyclic chemists from many different countries to contribute articles on their special fields. I am much indebted to all the authors for their interest and cooperation. In this volume, the attempt has been made to cover the literature to the end of 1961, and a not inconsiderable number of 1962 references do in fact occur.

My thanks are also due to members of the Editorial Board, especially Professor Adrien Albert to whom I owe a great debt of gratitude for his kindly advice and encouragement. The cooperation of Academic Press is appreciated.

A. R. KATRITZKY

Cambridge, England
October 1962

Contents

Contents of Volume 2

Recent Advances in the Chemistry of Thiophenes

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I. Introduction

In the development of thiophene chemistry three periods can be clearly distinguished; the Victor Meyer era, the Steinkopf period,[1] and the modern development starting with the discovery of the synthesis of thiophene from butane and sulfur,[2] making thiophene potentially available in unlimited amounts. Hartough in his well-known monograph,[3] has reviewed the intense and hectic thiophene research toward the end of the 1940's carried out mainly at the Socony-Vacuum laboratories, but also at many academic institutions. An article by Nord *et al.*[4] appeared in 1955 in which the research work in thiophene chemistry at Fordham University, as well as progress in general up to 1954, was reviewed.

During the first two periods interest was mainly focused on the substitution reaction of thiophenes. In particular, Steinkopf *et al.*[1] carried out a great deal of work on the preparation of the different isomers of simple thiophenes. Although interest in this area continued after the discovery of the new thiophene synthesis, especially in reactions more specific for the thiophene ring, the main aim was to introduce the thiophene ring in more complex organic molecules in order to obtain pharmacologically active or otherwise practically useful compounds. The large amount of work carried out in this direction is obvious from the recent review article by Martin-Smith and Reid[5] on biological activity in compounds possessing the thiophene ring. The conclusion of these authors is that all this work has shown small reward, if measured in terms of the number of new drugs of clearly superior clinical desirability which have been produced. However, these investigations have, in a somewhat unsystematic way, also increased our knowledge of the chemistry of thiophene.

During the last 5–6 years a new trend has been noticeable. The study of the reactivity of the thiophenic hydrogens and the influence

[1] W. Steinkopf, "Die Chemie des Thiophens." Theodor Steinkopff, Dresden und Leipzig, 1941.
[2] H. E. Rasmussen, R. C. Hansford, and A. N. Sachanen, *Ind. Eng. Chem.* **38**, 376 (1946).
[3] H. D. Hartough, "Thiophene and Its Derivatives." Interscience, New York, 1952.
[4] F. F. Nord, A. Vaitiekunas, and L. J. Owen, *Fortschr. chem. Forsch.* **3**, 309 (1955).
[5] M. Martin-Smith and S. T. Reid, *J. Med. Pharm. Chem.* **1**, 507 (1959).

of the thiophene nucleus on the reactivity of substituents have been attacked again with more quantitative methods. The whole arsenal of spectroscopic and other physical methods has been utilized in order to study the aromatic character of thiophene and the substituent effects in thiophenes. Metalation and halogen–metal interconversion reactions have been shown to be of great utility in the preparation of substituted thiophenes. Finally Raney nickel desulfurization has made thiophene compounds more and more important as intermediates for the preparation of aliphatic compounds.

It is the intention of the present author to discuss the aforementioned developments and not to give a complete review of all work concerning thiophenes which has appeared during the last 7–8 years. Because of the subjectivity inherent in choosing material for such a survey, it is possible that important contributions will unintentionally be overlooked for which the author would like to apologize.

II. Molecular Structure and Physical Properties of Thiophenes

A. Molecular Structure

1. *Quantum Chemical Calculations*

Since the time of the quantum-mechanical calculations by Longuet-Higgins,[6] many attempts have been made to calculate π-electron densities, resonance energies, dipole moments, and optical transitions both by the LCAO-MO and the valence bond method.[7–17] However, no agreement has been reached on the importance of *pd*-hybridization of the sulfur atom. This is considered by some workers an essential

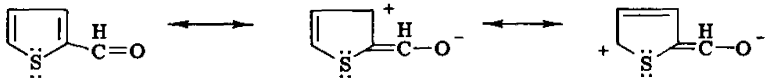
[6] H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).
[7] J. Metzger and F. Ruffler, *J. chim. phys.* **51**, 52 (1954).
[8] J. de Heer, *J. Am. Chem. Soc.* **76**, 4802 (1954).
[9] K. Kikuchi, *Sci. Repts. Tôhoku Univ., First Ser.* **40**, 133 (1956).
[10] K. Kikuchi, *Sci. Repts. Tôhoku Univ., First Ser.* **41**, 35 (1957).
[11] K. Maeda, *Sci. Repts. Tôhoku Univ., First Ser.* **43**, 203 (1959).
[12] K. Maeda, *Bull. Chem. Soc. Japan* **33**, 304 (1960).
[13] G. De Alti and G. Milazzo, *Univ. studi Trieste, Fac. sci., Ist. chim.* No. 24, p. 15 (1958).
[14] G. Milazzo and G. De Alti, *Rend. ist. super. sanità* **22**, 787 (1959).
[15] L. Melander, *Arkiv Kemi* **8**, 361 (1955).
[16] M. M. Krevoy, *J. Am. Chem. Soc.* **80**, 5543 (1958).
[17] A. Mangini and C. Zauli, *J. Chem. Soc.* p. 2210 (1960).

feature in the electronic structure of thiophene, making the sulfur atom similar to a CH=CH group, and being responsible for some of the differences between thiophene and furan and pyrrole; whereas others have suggested that most of the properties of thiophenes may be accounted for without invoking *pd*-hybridization at all,[16-18] Mangini and Zauli[17] even doubting the basic validity of the Longuet-Higgins approach. Different results have also been obtained regarding the relative π-electron densities in the α- and β-positions of thiophene,[9-12] which in the original Longuet-Higgins treatment[6] are equal. The greater free valence[8,18] and self-polarizability of the α-carbon,[8] the latter being related to Ingold's electromeric effect, are in accordance with the known greater reactivity of the α-position, which is also predicted by calculations on the localization energies of the quinoid transition states in aromatic substitution.[15,18]

Quantum-mechanical calculations on substituted thiophenes are still more difficult and localization energies and electronic charges have been calculated only for 2- and 3-nitrothiophene.[19,20]

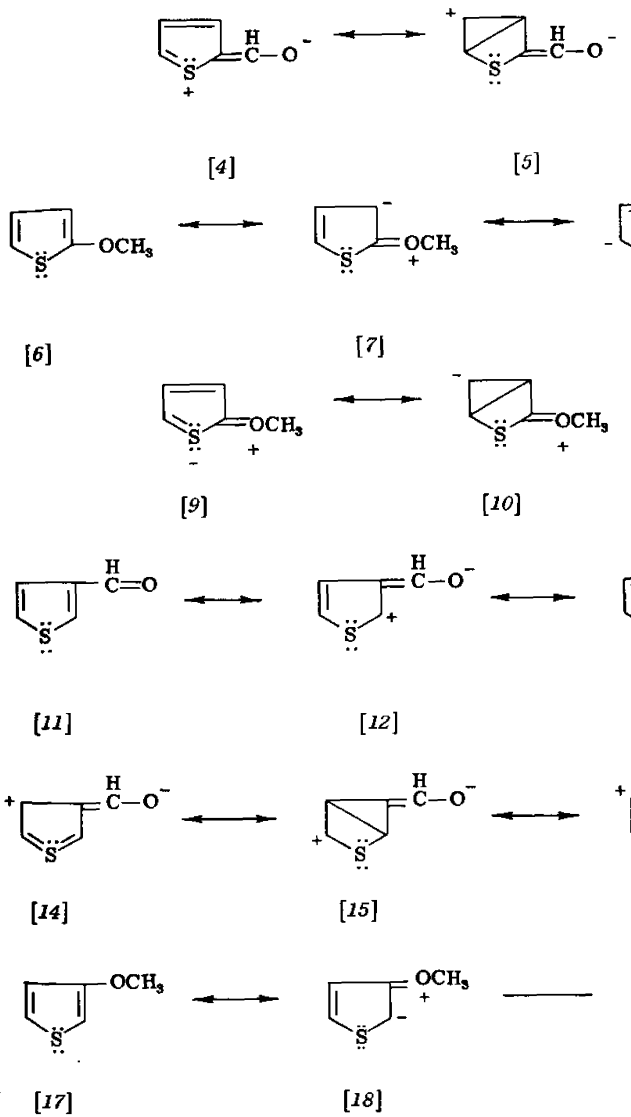
2. *Resonance Theory*

Gronowitz *et al.* have discussed the effects of substituents on chemical reactivity and on ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectra in terms of simple resonance theory.[21,22] They assume resonance structures **(1–5)** to contribute to a —I—M (Ingold's terminology) 2-substituted thiophene, resonance forms **(6–10)** to the structure of a ±I+M 2-substituted thiophene, forms **(11–16)** to a —I—M 3-substituted thiophene, and forms **(17–22)** to a ±I+M 3-substituted thiophene.



[1] [2] [3]

[19] F. L. Pilar and J. R. Morris, *J. Chem. Phys.* **34**, 389 (1961).
[20] L. Melander, *Acta Chem. Scand.* **9**, 1400 (1955).
[20] L. Melander, *Arkiv Kemi* **11**, 397 (1957).
[21] S. Gronowitz, *Arkiv Kemi* **13**, 295 (1958).
[22] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **16**, 539 (1960).



[4] [5]

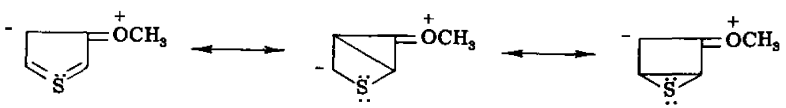
[6] [7] [8]

[9] [10]

[11] [12] [13]

[14] [15] [16]

[17] [18] [19]



[20] [21] [22]

Of these resonance forms, the classic ones (**1, 6, 11, 17**), although very important, give no information about the effect of substitution on the relative electron distribution. The others can be divided into four classes. Of greatest importance are those which contain only C—S single bonds and no "long bonds" (**2, 3, 7, 8, 12, 18**). Second in importance are those structures involving C=S double bonds and a positively charged sulfur (**4, 13**). Of minor weight are structures containing decets[22a] around the sulfur (**9, 14, 19, 20**), whereas structures with long bonds (**5, 10, 15, 16, 21, 22**) are considered to be almost negligible. The effects of some of these long-bond structures are identical with those of structures containing decets (cf. **14** with **16** and **20** with **22**). The order of relative importance of the various resonance structures is similar to that given by Schomaker and Pauling[23] in their classic study on the structure of thiophene itself. They suggested that the classic form should be given 70% weight, structures involving C=S double bonds and a positively charged sulfur 20%, and structures involving a decet on the sulfur were given a weight of 10%.

The foregoing resonance structures describe the influence of the substituents on the π-electron distribution in the thiophene ring. Besides this effect the inductive effect of the substituents on the σ-electron system must be considered when discussing physical and chemical properties of thiophenes.

Physical and chemical evidence supporting the theory mentioned in the foregoing will be given in the appropriate sections. Some predictions may be mentioned here. From resonance structures (**2, 3, 7, 8**) it is inferred that the substituent effect in 2-substituted thiophenes should be parallel to that in the corresponding benzenes, the 3- and 5-positions may be considered as *ortho* and *para* positions and the 4-position as a *meta* position. It is, however, obvious that the effect of a —M- and a +M-substituent are not simply reversed, as resonance structure (**4**) belonging to "class 2" is assumed to have a greater weight than (**9**). It is also expected from the low weights of structures such as (**14**), (**20**), (**16**), and (**22**), that the 4-position of 3-substituted thiophenes can hardly be expected to show the properties of an *ortho* position in the same way as in benzenes. Also for 3-substituted thiophenes differences in the effects of —M and +M substituents may be expected.

[22a] Ten electrons.

[23] V. Schomaker and L. Pauling, *J. Am. Chem. Soc.* **61**, 1769 (1939).

B. Spectroscopy of Thiophenes

1. *NMR Spectra*

The study of the NMR spectra of thiophenes has attracted considerable interest,[22,24-38b] partly because the spectra of substituted thiophenes containing only a few ring hydrogens are quite suitable for complete analysis and partly because in a series of related compounds the chemical shifts observed are related to differences in the electron distribution about chemically nonequivalent hydrogens (for review, see reference 39), especially for hydrogens far removed from the substituent.

[24] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **13**, 279 (1958).
[25] K. Takahashi, Y. Matsuki, T. Mashiko, and G. Hazato, *Bull. Chem. Soc. Japan* **32**, 156 (1959).
[26] S. Fujiwara, M. Katayama, S. Hayashi, H. Shimuzu, and S. Nishimura, *Bull. Chem. Soc. Japan* **32**, 201 (1959).
[27] J. B. Leane and R. E. Richards, *Trans. Faraday Soc.* **55**, 518 (1959).
[28] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **15**, 45 (1959).
[29] S. Gronowitz and R. A. Hoffman, *Acta Chem. Scand.* **13**, 1687 (1959).
[30] P. L. Corio and I. Weinberg, *J. Chem. Phys.* **31**, 569 (1959).
[31] R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **37**, 2095 (1959).
[32] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 501 (1960).
[33] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 515 (1960).
[34] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1960).
[35] T. Isobe, *Bull. Chem. Research Inst. Non-aqueous Solutions Tôhoku Univ.* **9**, 115 (1960).
[36] B. Dischler and W. Maier, *Z. Naturforsch.* **16a**, 318 (1961).
[37] S. Gronowitz, B. Gestblom, and R. A. Hoffman, *Acta Chem. Scand.* **15**, 1201 (1961).
[38] S. Gronowitz and B. Gestblom, *Arkiv Kemi* **18**, 513 (1962).
[38a] G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.* **83**, 5020 (1961).
[38b] K. Takahashi, Y. Matsuki, Y. Miyake, and G. Hazato, *Bull. Chem. Soc. Japan* **34**, 1599 (1961).
[39] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," pp. 271 ff. McGraw-Hill, New York, 1959.

The chemical shifts of the α- and β-hydrogens of thiophenes have been determined through a study of deuterated thiophenes[28] and also through complete interpretation of the complex thiophene spectrum.[28,31,36] The chemical shifts between the α- and β-hydrogens of the five-membered heterocyclics show the order furan > pyrrole > thiophene < selenophene as being 1.05 ppm,[35] 0.6 ppm,[40,41] 0.125 ppm,[28] and 0.57 ppm respectively.[35] The minimum at thiophene is in accordance with the fact that the aromatic character is greatest for this heterocycle. The fact that the resonances of the α-hydrogens occur at lower fields than those of the β-hydrogens in these heterocycles has been ascribed to lower electron density at the α-hydrogens.[40,42]

An investigation on 36 monosubstituted[22,33] and 65 disubstituted thiophenes[34] showed that the coupling constants, which are of equal sign,[28,33] fall in four distinct regions: $J_{35} = 1.25$–1.70 c/s; $J_{25} = 3.20$–3.65 c/s; $J_{34} = 3.45$–4.35 c/s; and $J_{45} = 4.90$–5.80 c/s. This reveals the outstanding suitability of NMR as a tool for the structure determination of disubstituted thiophenes[43,44] and also makes possible the assignment of each band in the NMR spectrum of a monosubstituted thiophene to a definite hydrogen.[24,25,27,33]

The chemical shifts of monosubstituted thiophenes relative to the α- and β-hydrogens of thiophene at infinite dilution in cyclohexane[22] are given in Table I and are discussed in the following.

The electron-withdrawing effect from the 3- and 5-positions in —I—M 2-substituted thiophenes, in accordance with resonance forms (2) and (3), is evident from the shifts toward lower field of the resonances of the 3- and 5-hydrogens. The shifts of the 5-hydrogens of COX 2-substituted thiophenes follow the mesomeric order of these substituents.[45] The chemical shifts of 2-thiocyanothiophene clearly reveal the electron-withdrawing effect of the SCN group which, although *ortho-para* directing, is strongly deactivating in electrophilic

[40] R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **37**, 1056 (1959).
[41] S. Gronowitz, A-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi* **18**, 133 (1961).
[42] E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Am. Chem. Soc.* **80**, 1204 (1958).
[43] S. Gronowitz, *Arkiv Kemi* **13**, 269 (1958).
[44] S. Gronowitz, P. Moses, A-B. Hörnfeldt, and R. Håkansson, *Arkiv Kemi* **17**, 165 (1961).
[45] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 77. Bell and Sons, London, 1949.

TABLE I
CHEMICAL SHIFTS (PPM) OF SUBSTITUTED THIOPHENES, RELATIVE TO THE SHIFTS OF THE α- AND β-HYDROGENS IN THIOPHENE

Substituent	Character	2-Substituted thiophenes			3-Substituted thiophenes		
		δ_3	δ_4	δ_5	δ_2	δ_4	δ_5
NO_2	−I−M	−0.82	+0.03	−0.30	−0.95	−0.60	−0.03
SO_2Cl	−I−M	−0.73	−0.06	−0.45	—	—	—
CN	−I−M	−0.47[a]	0.00	−0.28[a]	−0.63	−0.20	−0.15
CHO	−I−M	−0.65[a]	−0.10	−0.45[a]	−0.79	−0.45	−0.03
$COCH_3$	−I−M	−0.57	0.00	−0.28	−0.68	−0.47	+0.02
COC_2H_5	−I−M	−0.55	0.00	−0.28	−0.70	−0.48	+0.05
COCl	−I−M	−0.88	−0.06	−0.44	−1.05	−0.50	−0.03
CO_2CH_3	−I−M	−0.70	+0.05	−0.20	−0.78	−0.47	+0.05
SCN	−I(±M)	−0.30	+0.05	−0.28	−0.25	−0.05	−0.05
C≡CH	−I−M	−0.15	+0.16	+0.12	—	—	—
I	−I+M	−0.13	+0.33	−0.01	−0.06	0.00[a]	+0.19[a]
Br	−I+M	+0.05	+0.27	+0.11	+0.12	+0.08	+0.10
2-Thienyl	?	−0.08	+0.11	+0.15	—	—	—
SH	−I+M	0.00	+0.20	+0.07	+0.22[a]	+0.20[a]	+0.10[a]
SCH_3	−I+M	+0.03	+0.18	+0.05	+0.33	+0.10	+0.03
CH_3	+I+M	+0.37	+0.24	+0.28	+0.45	+0.22	+0.14
OCH_3	−I+M	+0.94	+0.43	+0.82	+1.10	+0.38	+0.20
OC_2H_5	−I+M	+0.92	+0.43	+0.81	—	—	—
$OC(CH_3)_3$	−I+M	+0.77	+0.38	+0.65	+0.78	+0.36	+0.22
NH_2	−I+M	+0.95	+0.45	+0.85	+1.25	+0.53	+0.25

[a] These resonances were not resolved.

substitution.[46] +M-Substituents cause shifts toward higher field especially of the 3- and 5-hydrogens, in accordance with resonance forms (7) and (8), the shifts of the 5-hydrogens following the known mesomeric order ($NH_2 > OCH_3 > CH_3$). The smaller upfield shift of the 5-hydrogen resonance in 2-*t*-butoxythiophene as compared to 2-methoxy- and 2-ethoxy-thiophene is ascribed to steric inhibition of resonance.[22] The fact that —M-substituents cause no shift of the 4-hydrogen in 2-substituted thiophenes or of the 5-hydrogen in 3-substituted compounds, whereas +M-substituents cause a noticeable upfield shift, has been ascribed to a relay of the charge of the 3- and 5-position (resonance forms 7 and 8) to the 4-position in a +M-substituted compound.[22] In —M-substituted compounds an alternative relay of the positive charge to the sulfur exists (resonance form 4),

[46] F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.* **78**, 854 (1956).

whereas an alternative relay of negative charge to the sulfur (resonance form 9) is less important.

The much larger shift of the 2-hydrogen compared to the 4-hydrogen in 3-substituted thiophenes are in complete agreement with the assumed weight of resonance forms (12) and (14) or (18) and (20). However, it is obvious from the high-field shift of hydrogen 4 in 3-methoxythiophene that resonance form (20) cannot be neglected and that *pd*-conjugation must, therefore, be considered in a more detailed discussion of the structure of thiophenes.[22]

The larger shifts of hydrogen 2 in 3-substituted thiophenes than those of hydrogen 3 in 2-substituted, have been ascribed to the greater probability of structures (12) and (18) over (2) and (7).

The SH, SCH_3, and weakly directing halogens cause small shifts, which to a large extent are determined by magnetic anisotropy effects, especially in the case of the halogens. Attempts have been made to estimate these effects for the other thiophenes.[22] Except for ortho-hydrogens, these effects are usually very small.

As can be seen from the present discussion, the electron distribution inferred from the chemical shifts of monosubstituted thiophenes is in good agreement with that expected on the basis of simple resonance theory.

In the benzene series, an approximately linear relationship has been obtained between the chemical shifts of the *para*-hydrogen in substituted benzenes[47-49] and Hammett's σ-values of the substituents. Attempts have been made, especially by Taft,[50,51] to use the chemical shifts as a quantitative characteristic of the substituent. It is more difficult to correlate the chemical shifts of thiophenes with chemical reactivity data since few quantitative chemical data are available (cf. Section VI,A). Comparing the chemical shifts of the 5-hydrogen in 2-substituted thiophenes and the parahydrogens in substituted benzenes, it is evident that although —I—M-substituents cause similar shifts, large differences are obtained for +M-substituents indicating that such substituents may have different effects on the reactivity of the two aromatic systems in question. Differences also

[47] P. Diehl, *Helv. Chim. Acta* p. 829 (1961).
[48] R. R. Fraser, *Can. J. Chem.* **38**, 2226 (1960).
[49] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.* **35**, 731 (1961).
[50] R. W. Taft, Jr., *J. Am. Chem. Soc.* **79**, 1045 (1957).
[51] R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.* **81**, 5352 (1959).

exist between the chemical shifts of thiophenes and the corresponding furans.[52] It is thus evident from chemical shift data that the influence of a substituent on the electron density varies from ring system to ring system.

The chemical shifts of the methyl groups of 5-substituted 2-methylthiophenes have been found to be approximately proportional to the shifts of the 2-ring hydrogen in 5-substituted thiophenes and thus dependent both on the mesomeric and on the inductive effects of the substituents.[38]

Spin-spin couplings of the order of 1 c/s between the side-chain hydrogens of methylthiophenes,[29,30,34] thiophenealdehydes,[25,27,29,34] thiophenealdoximes,[29] thiophenethiols,[34,53] and 2-thienylacetylene[33] and certain ring hydrogens have been observed. These side-chain couplings have the values of $J_{CH_3\text{-}3} = 1.00$–1.15 c/s, $J_{CH_3\text{-}4} = 0.2$–0.5 c/s, and $J_{CH_3\text{-}5} = 0.4$ c/s in 2-methylthiophenes; $J_{CH_3\text{-}2} = 0.9$–1.25 c/s and $J_{CH_3\text{-}4} = J_{CH_3\text{-}5} = 0.4$–$0.5$ c/s in 3-methylthiophenes; $J_{CHO\text{-}5} = 1.05$–1.40 c/s in 2-thiophenealdehydes; $J_{CHO\text{-}5} = (< 0.4)$–$0.80$ c/s in 3-thiophenealdehydes; $J_{SH\text{-}3} = 1.4$–1.6 c/s and $J_{SH\text{-}5} = 0.9$–1.0 c/s in 2-thiophenethiols; $J_{SH\text{-}2} = 0.65$–1.05 c/s and $J_{SH\text{-}5} = 0.3$ c/s in 3-thiophenethiols.[34] The characteristic pattern of these couplings have contributed to an understanding of the mechanisms behind spin-spin couplings.[34,54] These couplings are also useful for unambigous identification of ring hydrogens in disubstituted thiophenes.[34,44] Long-range couplings between protons of different side chains have been observed in the 3- and 5-methyl-2-thiophenthiols in 2-methyl-3-thiophenthiol as well as in 2,3-dimethylthiophene and substituted 2,3-dimethylthiophenes.[37]

2. *Microwave Spectra*

Through the careful investigation of Bak *et al.*[55,56] on the microwave spectra of thiophene, deuterated thiophenes[55] and 2- and 3-C^{13}-enriched thiophene,[57] the dimensions of thiophene (Table II) are

[52] S. Gronowitz, G. Sörlin, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi* **19**, 483 (1962).
[53] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **15**, 499 (1960).
[54] R. A. Hoffman, *Arkiv Kemi* **17**, 1 (1960).
[55] B. Bak, D. Christensen, J. Rastrup-Andersen, and E. Tannenbaum, *J. Chem. Phys.* **25**, 892 (1956).
[56] B. Bak, D. Christensen, L. Hansen Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectroscopy* **7**, 58 (1961).
[57] B. Bak, J. Christiansen, and J. T. Nielsen, *Acta Chem. Scand.* **14**, 1865 (1960).

known with very high precision. The high double-bond character of the C—S bond is especially striking and shows clearly how badly the

TABLE II
GEOMETRICAL PARAMETERS OF THIOPHENE FROM BAK'S *et al.* MICROWAVE INVESTIGATION[a]

Bond	Distance (Å)	Experimental uncertainty
C(2)H(2)	1.0776	±0.0015
C(3)H(3)	1.0805	±0.0014
C(2)S	1.7140	±0.0014
C(2)C(3)	1.3696	±0.0017
C(3)C(4)	1.4232	±0.0023
Bond	**Angle**	**Experimental uncertainty**
C(5)SC(2)	92°10′	±6′
SC(2)C(3)	111°28′	±14′
C(2)C(3)C(4)	112°27′	±11′
SC(2)H(2)	119°51′	±47′
C(4)C(3)H(3)	124°16′	±4′

[a] B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectroscopy* **7**, 58 (1961).

classic formula alone represents the true structure of the thiophene molecule. According to Bak, the higher double-bond character of the C—S bond as compared to the bond between C-3 and C-4 probably can be correlated with the greater chemical reactivity of the thiophenic carbon in electrophilic reactions.

3. *IR Spectra*

The characteristic bands in the IR spectra of thiophenes have been recorded.[58-60] 2-Substituted thiophenes show ring-stretching frequences at 1537–1509, 1444–1402, and 1365–1339 cm^{-1} which have been assigned to characteristic modes of vibration.[60] The hydrogen in-plane deformation bands occur at 1086–1077 and at 1053–1031 cm^{-1}. The

[58] A. Hidalgo, *Compt. rend. acad. sci.* **239**, 253 (1954).
[59] A. Hidalgo, *J. phys. radium* **16**, 366 (1955).
[60] A. R. Katritzky and A. J. Boulton, *J. Chem. Soc.* p. 3500 (1959).

bands at 938–905 and at 863–841 cm^{-1} are assigned to hydrogen-out-of-plane deformations. The band at 839–790 cm^{-1} is assigned to ring breathing.[60]

Many 3-substituted thiophenes have a characteristic absorption at 760–780 cm^{-1}.[61-64] Typical absorption bands exist for the different types of disubstituted thiophenes,[65] but no detailed study seems to have been published. The structures of such compounds, however, are much more simply determined by NMR spectroscopy (Section II,B,1).

The C=O absorption bands of 2-carbonyl substituted thiophenes such as 2-thiophenealdehyde and 2-acetylthiophene, always occur at lower frequencies than those of the corresponding 3-isomers,[21,62,66-68] because of the greater single-bond character of the C=O bond in 2-substituted compounds. This follows from the increased conjugation of the substituent in the 2-position over that in the 3-position as is evident from the resonance structures in Section II,A. The absorption shifts in 5-substituted 2-acetylthiophenes are in linear relation with Hammett's σ-values for the substituents.[67] The difference in the absorption frequencies of 2,5-dimethyl-3-acetylthiophene (1672 cm^{-1}) and 2,5-di-*t*-butyl-3-acetylthiophene (1684 cm^{-1}) may be ascribed to steric inhibition of resonance.[68] The Raman spectrum of 2-thiophenealdehyde shows two C=O lines at 1658 and 1675 cm^{-1}.[69] The characteristic absorption frequencies of the nitro group in the six isomeric bromonitrothiophenes occur at 6.52–6.63 and at 7.45–7.58 μ.[70]

The IR spectrum of thiophene in the region between 0.87–1.2 μ has been obtained.[71]

[61] S. Gronowitz, *Arkiv Kemi* **7**, 267 (1954).
[62] S. Gronowitz, *Arkiv Kemi* **11**, 519 (1957).
[63] S. Gronowitz, *Arkiv Kemi* **12**, 239 (1958).
[64] S. Gronowitz, and R. Håkansson, *Arkiv Kemi* **16**, 309 (1960).
[65] S. Gronowitz, P. Moses, and A.-B. Hörnfeldt, *Arkiv Kemi* **17**, 237 (1961).
[66] S. Gronowitz and A. Rosenberg, *Arkiv Kemi* **8**, 23 (1955).
[67] Y. Otsuji and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1199 (1959); *Chem. Abstr.* **55**, 3194 (1961).
[68] V. P. Litvinov and V. A. Morozow, *Izvest. Akad. Nauk. SSSR. Otdel. Khim. Nauk* p. 166 (1961).
[69] P. Chiorbili and A. M. Drusiani, *Atti. accad. nazl. Lincei, Rend. Classe sci. fis. mat. nat.* **12**, 309 (1952); *Chem. Abstr.* **48**, 9197 (1954).
[70] R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi* **78**, 954 (1957); *Chem. Abstr.* **54**, 14224 (1960).
[71] M. Aumeras, B. Laugrost, and R. Minangoy, *Bull. soc. chim. France* p. 311 (1952).

4. *UV Spectra*

The study of the UV spectra of thiophenes has attracted considerable interest during the last years. Many attempts have been made to calculate the optical transitions of thiophene[13,14,17] in order to assign the three bands at 240.5, 232.6, and 220.4 mμ in the UV spectrum of gaseous thiophene[72] to definite transitions.[72-74] The spectrum of thiophene in solution shows a broad band at about 220–250 mμ (log $\epsilon \approx 3.9$) with few special features.[75]

The aforementioned conditions make an analysis of the effect of substituents in thiophene on the UV spectrum more difficult than in the benzene series. In benzene there are two widely separated areas of absorption with different intensities. In thiophene there are instead two or three absorption bands due to electronic transitions which overlap and are of similar intensity. Finally, two very low-intensity bands at 313 and 318 mμ have been found in thiophene.[76]

Although the UV spectra of a large number of substituted thiophenes have been recorded by many authors during recent years,[70,77-82] the first systematic studies of the UV spectra of monosubstituted thiophenes designed to obtain information about differences in the influence of substituents in 2- and 3-substituted thiophenes were carried out independently by Andrisano and Pappalardo[83] and by the present author.[84]

The UV spectra of —I—M 2-substituted thiophenes show two almost overlapping high-intensity bands both of which are displaced, with increasing conjugating power of the substituent, toward longer wavelengths. The extinction increases in the same order as in the

[72] G. Milazzo, *Gazz. chim. ital.* **78**, 835 (1948).
[73] G. Milazzo, *Gazz. chim. ital.* **83**, 787 (1953).
[74] J. Sicé, *J. Phys. Chem.* **64**, 1573 (1960).
[75] H. D. Hartough, "Thiophene and Its Derivatives," pp. 101–102. Interscience, New York, 1952.
[76] M. R. Padhye and S. R. Desay, *Proc. Phys. Soc. (London)* **65A**, 298 (1952).
[77] H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.* **73**, 4521 (1951).
[78] E. Campaigne and J. L. Diedrich, *J. Am. Chem. Soc.* **73**, 5240 (1951).
[79] F. S. Boig, G. W. Costa, and I. Osvar, *J. Org. Chem.* **18**, 775 (1953).
[80] J. Sicé, *J. Am. Chem. Soc.* **75**, 3697 (1953).
[81] P. Ramart-Lucas, *Bull. soc. chim. France* p. 1017 (1954).
[82] H. H. Szmant and C. McGinnis, *J. Am. Chem. Soc.* **74**, 240 (1952).
[83] R. Andrisano and G. Pappalardo, *Spectrochim. Acta* **12**, 350 (1958).
[84] S. Gronowitz, *Arkiv Kemi* **13**, 239 (1958).

benzene series ($NO_2 > CHO > COCH_3 > COOH > CN > SO_2CH_3$). The two bands have been interpreted by analogy with the benzene series in terms of a progressive displacement of the 215- and 235-mμ transitions which correspond to the 203- and 254-mμ transitions in benzene.[84] The displacements of the low-wavelength (primary) band of thiophenes are of the same order of magnitude as those in the corresponding benzenoid compounds.[84] The ratio of the wavelength of the secondary band to that of the primary band in these thiophenes is constant, as is the case in the benzene series. Mangini and Tundo[85] attribute the primary band of thienyl ketones to an excitation in the thienyl group (N-V transition of π-π^* type), whereas the secondary absorption band arises from excitation of the thienyl–carbonyl chromophore. The effect of *ortho* substituents on the spectra of 2-benzoyl and 2,5-dibenzoylthiophenes is ascribed to steric hindrance of the phenyl–carbonyl group interaction.[85]

The —I—M 3-substituted thiophenes in alcohol show only one band, and, as is found in the 2-isomer, this is displaced (with increased extinction) toward longer wavelength with increasing conjugating power of the substituent.[84] It is probable that this is the displaced 235-mμ band of thiophene, since the spectra of 3-acetylthiophene and 3-cyanothiophene also show a primary band at about 225 mμ in hexane solution.[86]

The smaller bathochromatic shift of the thiophene chromophore in 3-substituted thiophenes compared with that of the 2-isomers gives additional evidence that the 2-position in thiophenes affords more effective conjugation than the 3-position.[83,84,86]

Thiophenes substituted with groups such as alkyl, halogens, OCH_3, and SCH_3 show small but characteristic differences between 2- and 3-substituted compounds.[84] In these cases, however, it is the 2-isomer which shows the less complex spectrum. Thus, 2-substituted alkylthiophenes and halothiophenes show a single band with greater extinction than the 3-isomers whose spectra exhibit two peaks in a broadened absorption band.[84,87] These differences are also present in the spectra of 2,5- and 3,4-dihalosubstituted compounds.[87] In 2-substituted thiophenes, the intensity of the band varies inversely as the electronega-

[85] A. Mangini and A. Tundo, *Z. Electrochem.* **64**, 694 (1960).
[86] Y. Sugimoto, S. Nishimura, and E. Imoto, *Bull. Univ. Osaka Prefect., Ser. A* **8**, 71 (1959).
[87] J. Degani, A. Tundo and C. Zauli, *Boll. sci. fac. chim. ind. Bologna* **19**, 76 (1961).

tivity of the substituent, decreasing in the order 2-iodo-, 2-bromo-, and 2-chloro-thiophene. This is diametrically opposite from the effect observed in the corresponding benzene derivatives and the 3-substituted thiophenes.[87,88] Larger displacements occur when stronger auxochromes such as the OCH_3 or SCH_3 groups are attached to the thiophene nucleus.[84,87]

The effect of interposing a —CH=CH— group in 2-thiophene carbonyl derivatives, such as those of carboxylic acids, esters, aldehydes, and methyl ketones, has been studied by comparing the resulting spectra with those of the corresponding 2-thienylacrylic acid derivatives.[89] The results demonstrate a bathochromic shift of about 25 mμ for the primary band (often appearing as an inflection) and of about 40 mμ of the secondary band. The change in transition energy produced by interposing a —CH=CH— group (≈13 kcal/mole) was smaller than for the corresponding furans (≈19 kcal/mole).[89] The effect on the spectra of a bromine or nitro group in the 5-position of both types of compounds has also been investigated.[89,90] The bathochromic shift arising from the introduction of the NO_2 group was inversely proportional to the —M effect of the C=O group.[90]

The spectra of 2- and 3-phenylthiophene[91,92] and 2,5- and 3,4-diarylthiophenes[93] have recently been studied.

Systematic studies on disubstituted thiophenes are scarce, but some differences between the various series of disubstituted thiophenes have been detected.[77,80] According to Imoto *et al.*, the main effect of substituents in 2,5-disubstitution in thiophenes appears in the wavelength shift, whereas the main effect of substituents in the 2,4-disubstituted thiophenes appears in the intensity changes of the bands.[86] The intensities of the first absorption band of some 2,5-disubstituted thiophenes have been calculated[86] from the spectroscopic moments of the substituents.[94] The UV absorption of thiophene was displaced

[88] J. Sicé, *J. Phys. Chem.* **64**, 1572 (1960).
[89] G. Pappalardo, *Gazz. chim. ital.* **89**, 540 (1959).
[90] G. Pappalardo, *Gazz. chim. ital.* **89**, 551 (1959).
[91] B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.* **72**, 3379 (1950).
[92] L. Bruzzi, J. Degani, and A. Tundo, *Boll. sci. fac. chim. ind. Bologna* **19**, 40 (1961).
[93] J. Degani, A. Tundo, and C. Zauli, *Boll. sci. fac. chim. ind. Bologna* **19**, 50 (1961).
[94] J. R. Platt, *J. Chem. Phys.* **19**, 263 (1951).

toward lower frequency on methyl substitution,[88] and the oscillator strength has been calculated for several methylthiophenes.[88] The UV data for a number of simple monosubstituted thiophenes are collected in Table III.

TABLE III
UV SPECTRAL DATA FOR SOME MONOSUBSTITUTED THIOPHENES IN ALCOHOL

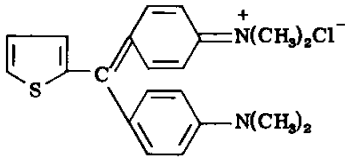
Substituents	λ_{max} (mμ)	log ε	Ref.
H	215, 231	3.8, 3.87	*a*
2-NO_2	270, 296	3.80, 3.78	*a*
2-CHO	260, 286	4.04, 3.86	*a*
2-$COCH_3$	260, 283	4.01, 3.87	*a*
2-COOH	246, 260	3.96, 3.84	*a*
2-CN	243, 258	3.97, 3.80	*a*
2-SO_2CH_3	233, 252	3.89, 3.77	*a*
2-CO_2CH_3	248, 268	3.97, 3.86	*b*
2-$CO_2C_2H_5$	249, 269	3.95, 3.89	*b*
2-$CONH_2$	248, 272	3.78, 3.87	*b*
2-Br	236	3.90	*a*
2-OCH_3	229, 243	3.61, 3.69	*a*
2-SCH_3	236, 273	3.76, 3.58	*a*
2-$NHCOCH_3$	264	4.01	*c*
3-CHO	251	4.12	*a*
3-$COCH_3$	250	4.08	*a*
3-COOH	241	3.92	*a*
3-CO_2CH_3	240.5	3.95	*b*
3-$CO_2C_2H_5$	240	3.95	*b*
3-$CONH_2$	241	3.89	*b*
3-Br	232, 241	3.61, 3.65	*a*
3-OCH_3	221, 253	3.59, 3.59	*a*
3-SCH_3	216, 269	3.70, 3.56	*a*
3-$NHCOCH_3$	257.5	3.77	*c*

[a] S. Gronowitz, *Arkiv Kemi* **13**, 239 (1958).
[b] R. Andrisano and G. Pappalardo, *Spectrochim. Acta* **12**, 350 (1958).
[c] Y. Sugimoto, S. Nishimura, and E. Imoto, *Bull. Univ. Osaka Perfect., Ser. A*, **8** 71 (1959).

The replacement of a benzene nucleus by a thiophene nucleus in compounds containing other chromophores causes more or less pronounced bathochromic shifts. These effects have been noticed in the thiophene analogs of malachite green (**23**),[95,96] in cumulenes such as

[95] C. D. Mason and F. F. Nord, *J. Org. Chem.* **16**, 722 (1951).
[96] V. V. Ghaisas, B. J. Kane, and F. F. Nord, *J. Org. Chem.* **23**, 560 (1958).

the red 1,4-diphenyl-1,4-di(2-thienyl)butatriene (24),[97] in 1-(2-thienylmethylene)guaiazulenium perchlorate (25),[98] and in a thienyl substituted diformazane (26), which is blue in contrast to the red phenyl



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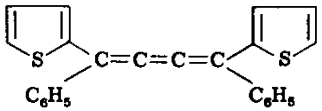

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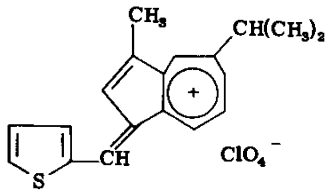

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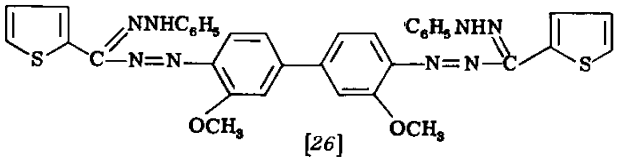


[26]

analog.[99] The bathochromic shifts are ascribed to the superior electron-releasing power of the 2-thienyl nucleus.[95,96,98]

Of interest in this connection is a study of the UV spectra of chalcones of the general type A—CH=CH—CO—B, where A and B are 2-thienyl, 2-furyl, and phenyl in all combinations.[77,100] The 2-thienyl group causes a bathochromic shift in both the A- and B-positions,

[97] R. Kuhn and J. Jahn, *Chem. Ber.* **86**, 759 (1953).
[98] E. C. Kirby and D. H. Reid, *J. Chem. Soc.* p. 494 (1960).
[99] W. Ried and H. Gick, *Ann. Chem. Liebigs* **581**, 16 (1953).
[100] H. H. Szmant and H. J. Planinsek, *J. Am. Chem. Soc.* **76**, 1193 (1954).

showing that it is both a better electron-releasing and a better electron-donating group than the benzene ring.

The spectra and halochromism of thiophene analogs of triphenyl and diphenyl carbinol,[101] the spectra of anilides of 2- and 3-thenoylacetic acid,[102] and the fluorescence of some thiophene compounds[103] have been investigated.

C. Thermochemical and Other Properties

The thermodynamic properties of thiophene,[104] 2-methylthiophene,[105] and 3-methylthiophene[106] have been computed from careful measurements of the heat capacity of the solid, liquid, and vapor states, the heat of fusion, the heat of vaporization, and the heat of combustion. From the heat of combustion of thiophene[107] and from thermochemical bond energies, the resonance energy of thiophene has been re-estimated to be only 20 kcal/mole.

The reduction of the C—Br and C—I group moments from 1.10 and 0.90 in bromo- and iodo-benzene to about 0.80 and 0.50 in 2-bromo- and 2-iodo-thiophene has been ascribed to the larger weight of resonance forms such as (8) and (9) in the thiophene series.[108]

The chlorine, nuclear, quadrupole, resonance frequencies of chloro-substituted thiophenes are much higher than those of the corresponding benzene derivatives. This has been ascribed to a relayed inductive effect originating in the polarity of the C—S σ-bond in thiophenes.[109]

The refractive indices, densities, and surface tension of thiophene, alkyl- and halo-thiophenes, and of some other derivatives have been

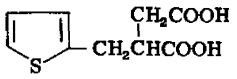
[101] V. F. Lewrushin, S. V. Tsukerman, and I. G. Syrovatka, *Zhur. Obshchei Khim.* **31**, 1275 (1961).
[102] N. S. Vul'fson and V. E. Kolchin, *Zhur. Obshchei Khim.* **30**, 3425 (1960); *Chem. Abstr.* **55**, 19892 (1961).
[103] R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi*, **78**, 965 (1957); *Chem. Abstr.* **54**, 14224 (1960).
[104] W. N. Hubbard, D. W. Scott, F. R. Frow, and G. Waddington, *J. Am. Chem. Soc.* **77**, 5855 (1955).
[105] R. E. Pennington, H. L. Finke, W. N. Hubbard, J. F. Messerly, F. R. Frow, I. A. Hossenlopp, and G. Waddington, *J. Am. Chem. Soc.* **78**, 2055 (1956).
[106] J. P. McCullough, S. Sunner, H. L. Finke, W. N. Hubbard, M. E. Gross, R. E. Pennington, J. F. Messerly, W. D. Good, and G. Waddington, *J. Am. Chem. Soc.* **75**, 5075 (1953).
[107] S. Sunner, *Acta Chem. Scand.* **9**, 847 (1955).
[108] M. T. Rogers and T. W. Campbell, *J. Am. Chem. Soc.* **77**, 4527 (1955).
[109] M. J. S. Dewar and E. A. C. Lucken, *J. Chem. Soc.* p. 426 (1959).

determined.[110] The parachors, molecular refractions, and molecular refraction coefficients have been evaluated from the new experimental data.[110]

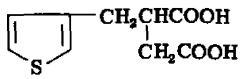
D. Optical Activity

1. *Central Asymmetric Thiophenes*

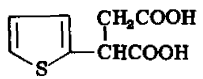
The pronounced influence of the phenyl group on optical activity led Fredga and Palm[111] to initiate an investigation on the optical activity of thiophene derivatives, in order to use this physical property for the elucidation of the aromatic character of thiophene. 2- (**27**)[111] and 3-Thenylsuccinic acid (**28**),[112] 2- (**29**)[113] and 3-thienylsuccinic acid (**30**),[114] 2- (**31**)[115] and 3-thienylglycolic acid (**32**),[116] 2- (**33**) and 3-α-methoxythienylacetic acid (**34**),[117] α-phenyl 2-thienylglycolic acid (**35**),[118] α-(2-thienyl)-β-phenylpropionic acid (**36**),[119] α-phenyl-β-(2-thienyl)propionic acid (**37**),[119] α,β-di(2-thienyl)propionic acid (**38**)[120] have been resolved into antipodes with the help of optically active bases.



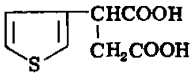
[*27*]



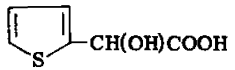
[*28*]



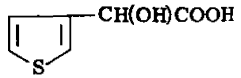
[*29*]



[*30*]



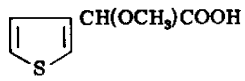
[*31*]



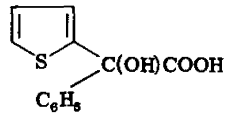
[*32*]

[110] G. H. Jeffery, R. Parker, and A. I. Vogel, *J. Chem. Soc.* p. 570 (1961).
[111] A. Fredga and O. Palm, *Arkiv Kemi, Mineral. Geol.* **A26**, No. 26 (1949).
[112] S. Gronowitz and S. Larsson, *Arkiv Kemi* **8**, 567 (1955).
[113] K. Pettersson, *Arkiv Kemi* **7**, 39 (1954).
[114] S. Gronowitz, *Arkiv Kemi* **11**, 361 (1957).
[115] S. Gronowitz, *Arkiv Kemi* **13**, 87 (1958).
[116] S. Gronowitz, *Arkiv Kemi* **13**, 231 (1958).
[117] T. Raznikiewicz, *Arkiv Kemi* **18**, 467 (1961).
[118] A. Fredga, K. Aejmeleaus, and B. Tollander, *Arkiv Kemi* **3**, 331 (1951).
[119] K. Pettersson, *Arkiv Kemi* **7**, 279 (1954).
[120] K. Pettersson, *Arkiv Kemi* **7**, 339 (1954).

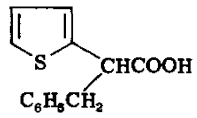
[*33*]



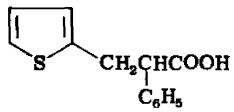
[*34*]



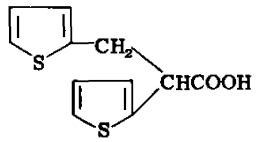
[*35*]



[*36*]



[*37*]



[*38*]

The quasi racemate method[121] proved very useful for the steric correlation of these compounds with the corresponding benzene derivatives,[111,112,114–116,122–124] as geometrically the differences between these groups are so small that the limits of isomorphic exchangeability are not often exceeded.[112] This confirms the view that the largest similarity between the thiophenes and benzenes is related to such physical properties as shape, size, and molecular weight, which, for instance, are reflected in the melting and boiling points.

In addition, the steric configuration can be obtained by Raney nickel desulfurization to optically active aliphatic acids of known configuration.[113,115,125,126] Combined with the quasi racemate method this

[121] A. Fredga, *Tetrahedron* **8**, 126 (1960).
[122] K. Pettersson, *Arkiv Kemi* **7**, 347 (1954).
[123] K. Pettersson, *Arkiv Kemi* **8**, 387 (1955).
[124] K. Pettersson, *Arkiv Kemi* **10**, 297 (1956).
[125] A. Fredga, *Arkiv Kemi* **6**, 277 (1953).
[126] K. Pettersson, *Arkiv Kemi* **9**, 509 (1956).

gives an elegant method for determining the configuration of benzene derivatives.[125] In this way the absolute configuration of mandelic acid was confirmed.[115]

The rotatory power of the thiophene compounds (Table IV) is

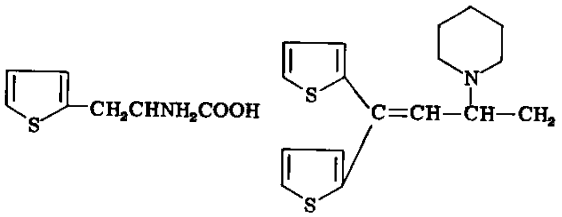
TABLE IV
ROTATION VALUES FOR THIENYLSUBSTITUTED CARBOXYLIC ACIDS IN ETHANOL

Compound	$[M]_D^{25}$
2-Thenylsuccinic acid (**27**)	16.5°
3-Thenylsuccinic acid (**28**)	32.1°
2-Thienylsuccinic acid (**29**)	206°
3-Thienylsuccinic acid (**30**)	205°
2-Thienylglycolic acid (**31**)	140°
3-Thienylglycolic acid (**32**)	162°
α-Methoxy-2-thienylacetic acid (**33**)	193°
α-Methoxy-3-thienylacetic acid (**34**)	207°
α-Phenyl-β-(2-thienyl)propionic acid (**36**)	265°
α-(2-Thienyl)-β-phenylpropionic acid (**37**)	181°
α,β-di-(2-Thienyl)propionic acid (**38**)	196°

somewhat smaller than that of the phenyl analogs (being largest for the 3-isomers) and has been discussed in terms of the Kuhn-Freudenberg theory.[21] Similarly to the benzene ring, the thiophene ring is a dominant substituent, the main contribution to the rotation in the visible region arising from the anisotropy of the 235-mμ band.[21] The rotatory dispersion curves of (**27**)–(**30**) and (**36**)–(**38**) are all of the plain type,[127] but they indicate that the lower rotation values in the visible region are due to the shorter absorption wavelength of the anisotropic band.[127]

The biologically important anti-β-phenylalanine, β-2-thienylalanine (**39**), has been resolved into antipodes through enzymatic resolution with carboxypeptidase.[128,129] The pharmacologically important 3-piperidino-1,1-bis-2-thienyl-1-butene (**40**), which crystallizes as a conglomerate, has been resolved by hand picking.[130]

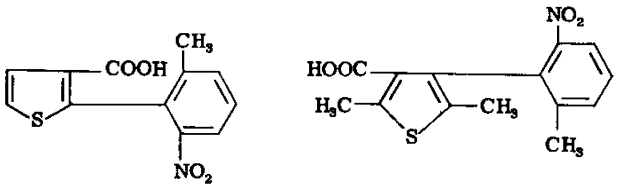
[127] B. Sjöberg, *Acta Chem. Scand.* **14**, 273 (1960).
[128] F. W. Crowe and F. F. Nord, *Arch. Biochem.* **25**, 460 (1950).
[129] B. F. Dunn, *J. Biol. Chem.* **234**, 802 (1959).
[130] R. Kimura and T. Yabuuchi, *Chem. & Pharm. Bull. (Tokyo)* **7**, 171 (1959); *Chem. Abstr.* **54**, 22625 (1960).



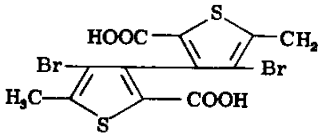
[*39*] [*40*]

2. *Axial Asymmetric Thiophenes*

Optical activity owing to restricted rotation (atropisomerism) has been demonstrated in two phenylthiophenes: 2-(6-methyl-2-nitrophenyl)-3-thiophenecarboxylic acid (**41**),[131] which rapidly racemized in solution, and 2,5-dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thiophenecarboxylic acid (**42**),[132] which was optically stable (at room temperature). Recently the first bithienyl, 2,2′-dicarboxy-4,4′-dibromo-5,5′-dimethyl-3,3′-bithienyl (**43**), has been resolved into optical antipodes[133,133a] which were optically stable.



[*41*] [*42*]



[*43*]

[131] L. J. Owen and F. F. Nord, *J. Org. Chem.* **16**, 1864 (1951).
[132] G. N. Jean, *J. Org. Chem.* **21**, 419 (1956).
[133] S. Gronowitz and H. Frostling, *Tetrahedron Letters* p. 604 (1961).
[133a] S. Gronowitz and H. Frostling, *Acta Chem. Scand.* **16**, 1127 (1962).

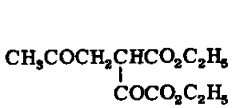
III. Preparation of Thiophenes

A. By Means of Ring-Closure Reactions

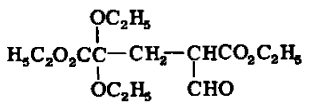
Although the present rapid development of thiophene chemistry is owing to the commercial availability of thiophene, many thiophene derivatives can still advantageously be prepared by means of ring-closure reactions instead of by a complex series of substitution reactions starting with thiophene.

The classic dry distillation of sodium succinate and P_2S_3 has been modified to give thiophene in 45% yield on a rather large scale.[134] Another example of the reaction of 1,4-dicarbonyl compounds with phosphorus sulfides is the preparation of authentic 2-*t*-butyl-5-methylthiophene in 53% yield from 6,6-dimethylheptadione-2,5 and P_2S_5.[135] More complex cases are the reactions of ethyl 2-ethoxalyl-4-ketovalerate (**44**) and diethyl α,α-diethoxy-α'-formylglutarate (**45**) with P_2S_5 in boiling toluene which yield 5-methyl-2,3-thiophenedicarboxylic acid (**46**)[136] and 2,4-thiophenedicarboxylic acid (**47**),[137] respectively.

Similarly 3,4-thiophenedicarboxylic acid has been prepared by the



[*44*]

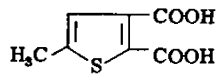


[*45*]

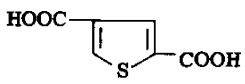
reaction of diethyl 1-formyl-2-diethoxymethylsuccinate with P_2S_5 in toluene.[137a] Attempts to obtain 2,3-thiophenedicarboxylic acid in an analogous way from 2-ethoxalyl-4,4-diethoxybutyronitrile (**48**) gave (**49**) as the main product.[136]

The reaction of 1,2-dibenzoylethane with hydrogen sulfide and hydrogen chloride in chloroform, with zinc chloride as a catalyst, gives 2,5-diphenylthiophene in high yield and is claimed to be better than the classic P_2S_5 method.[138]

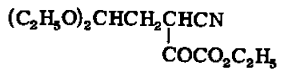
[134] I. Hirao, *Yakugaku Zasshi* **73**, 1023 (1953); *Chem. Abstr.* **48**, 10723 (1954).
[135] N. Messina and E. V. Brown, *J. Am. Chem. Soc.* **74**, 920 (1952).
[136] R. G. Jones, *J. Am. Chem. Soc.* **77**, 4069 (1955).
[137] R. G. Jones, *J. Am. Chem. Soc.* **77**, 4074 (1955).
[137a] E. C. Kornfeld and R. G. Jones, *J. Org. Chem.* **19**, 1671 (1954).
[138] E. Campaigne and W. O. Foye, *J. Org. Chem.* **17**, 1405 (1952).



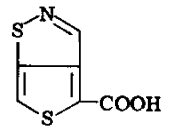
[*46*]



[*47*]



[*48*]



[*49*]

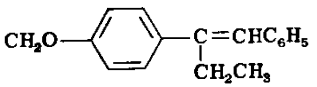
Substituted thiophenes, such as 2-iodo-, 2-bromo-, 2-chloromethyl-, and 2-acetyl-thiophene have been obtained by reacting crude, coal-tar benzene with the appropriate reagents.[139]

The reaction of olefins,[140] alcohols,[141,142] and epoxides[143,144] with H_2S[141,143,144] or SO_2[140,142] at high temperatures over catalysts such as Al_2O_3 or Cr_2O_3–Al_2O_3 has been used for the preparation of simple thiophenes in moderate yields.

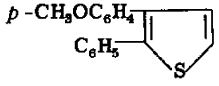
Of greater importance is the reaction of unsaturated compounds with sulfur at 200–250°C, which normally leads to 1,2-dithiole-3-thiones (trithiones) but especially with 2-arylsubstituted 2-butenes and 1- aryl- or 2-aryl-1-butenes, thiophenes are obtained in 15–60% yield.[145–149] Thus *p*-methoxy-α-ethylstilbene (**50**) gives 2-phenyl-3-

[139] R. Motoyama and E. Imoto, *Kôgyô Kagaku Zasshi* **55**, 460 (1952); *Chem. Abstr.* **48**, 13681 (1954).
[140] Yu. K. Yur'ev and L. L. Khmel'nitskii, *Doklady Akad. Nauk S.S.S.R.* **92**, 101 (1953); *Chem. Abstr.* **48**, 10725 (1954).
[141] Yu. K. Yur'ev, K. Yu. Novitskii, and E. V. Kukharskaya, *Doklady Akad. Nauk S.S.S.R.* **68**, 541 (1949); *Chem. Abstr.* **44**, 1020 (1950).
[142] Yu. K. Yur'ev and L. I. Khmel'nitskii, *Zhur. Obshchei Khim.* **23**, 1725 (1953); *Chem. Abstr.* **48**, 13680 (1954).
[143] Yu. K. Yur'ev and K. Y. Novitskii, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **22**, 2243 (1952).
[144] M. S. Malinovskii, *Ukrain. Khim. Zhur.* **16**, 351 (1950); *Chem. Abstr.* **48**, 11415 (1954).
[145] M. G. Voronkov, A. S. Broun, G. B. Karpenko, and B. L. Golshtein, *Zhur. Obshchei Khim.* **19**, 1356 (1949).
[146] J. Schmitt and A. Lespagnol, *Bull. soc. chim. France* p. 459 (1950).

p-methoxyphenylthiophene (**51**) upon reaction with sulfur.[148] 1-Phenyl-3-*p*-methoxyphenyl-2-butene (**52**) gives 2-phenyl-4-*p*-methoxyphenylthiophene (**53**)[149] in 21% yield whereas 1-*p*-methoxyphenyl-3-phenyl-2-butene gives 2-*p*-methoxyphenyl-4-phenylthiophene in 53% yield.[149] In the same way, 2- and 3-phenylthiophene[145] and the

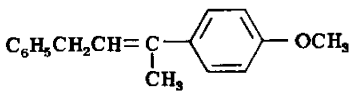


[*50*]



[*51*]

three isomeric methyl-2-phenylthiophenes[147] have been obtained. The yields with monoarylbutenes are usually lower than with the diaryl compounds. The reaction of alloocimene (**54**) with sulfur gives a



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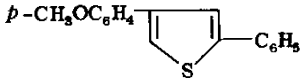
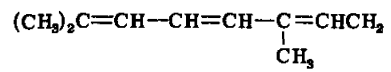


[*53*]

mixed thiophene-1,2-dithiole-3-thione (**55**),[150] which, upon treatment with permanganate and alkali, yields 4,5-dimethyl-2-thiophenecarboxylic acid. The reaction of esters of acrylic, fumaric, and crotonic acids with sulfur at 150–200°C leads to thiophene derivatives.[151] Dimethyl maleate and dimethyl fumarate gave tetramethyl thiophenetetracarboxylate in 20% yield.[151] Tetrachlorothiophene has been prepared in quantitative yield by the reaction of hexachlorobutadiene with sulfur.[151a]

[147] M. G. Voronkov and B. L. Golshtein, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **20**, 1263 (1950).
[148] J. Schmitt, R. Fallard, and M. Suquet, *Bull. soc. chim. France* p. 1147 (1956).
[149] W. E. Parham and E. T. Harper, *J. Am. Chem. Soc.* **82**, 4936 (1960).
[150] N. Lozach and Y. Mollier, *Bull. soc. chim. France* p. 1389 (1959).
[151] H. Hopff and J. von der Crone, *Chimia* (*Switz.*) **13**, 107 (1959); *Chem. Abstr.* **54**, 1484 (1960).
[151a] E. J. Geering, *J. Org. Chem.* **24**, 1128 (1959).



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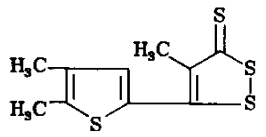
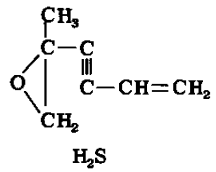


[*55*]

The Bogert synthesis of 2,4-diarylthiophenes consisting of the reaction of sulfur with the anils of arylalkyl ketones, has been shown to lead to a mixture of 2,4- and 2,5-disubstituted thiophenes.[152]

The ease with which thiophenes are formed in the reaction of acetylenic epoxides[153–155] and of polyacetylenes[156] with hydrogen sulfide is of great interest in connection with the biosynthesis of the naturally occurring thiophenes (cf. Section VIII,A) and also of preparative importance. 2-Methyl-1,2-oxido-5-hexene-3-yne (**56**) in water containing barium hydroxide reacts with H_2S at 50°C to give 4-



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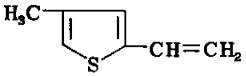
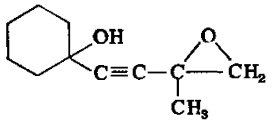


[*57*]

methyl-2-vinylthiophene (**57**) in 75% yield.[153] Similarly 3-methyl-2,3-epoxy-6-heptene-4-yne yielded 2-vinyl-4,5-dimethylthiophene upon reaction with H_2S.[153] The presence of the vinyl group is not necessary. Thus, 2-ethyl-1,2-epoxy-3-pentyne gave 2-methyl-4-ethylthiophene, and 3-methyl-2,3-oxido-4-hexyne gave 2,3,5-trimethylthiophene with the same good yield.[153] The reaction has also been applied to hydroxy-substituted acetylenic epoxides—2-methyl-(4-hydroxycyclohexyl)-1,2-oxido-3-butyne (**58**) gave (**59**) which dehydrated to 2-(1-cyclohexenyl)-4-methylthiophene.[154] The Perveev reac-

[152] P. Demerseman, N. P. Buu-Hoi, R. Royer, and A. Cheutin, *J. Chem. Soc.* p. 2720 (1954).
[153] F. Ya. Perveev and N. Y. Kudryashova, *Zhur. Obshchei Khim.* **23**, 976 (1953); *Chem. Abstr.* **48**, 8219 (1954).
[154] F. Ya. Perveev and T. N. Kurengina. *J. Gen. Chem. USSR.* (*Engl. Transl.*) **25**, 1579 (1955).



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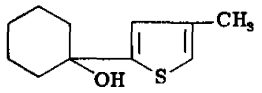
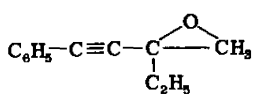
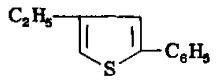


[59]

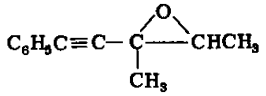
tion has also been extended to the preparation of phenylthiophenes.[155] 2-Phenyl-4-ethylthiophene (**61**) was, for example, obtained in 66% yield from 1-phenyl-3-ethyl-3,4-epoxy-1-butyne (**60**) and, similarly, 4,5-dimethyl-2-phenylthiophene from 1-phenyl-3-methyl-3,4-epoxy-1-pentyne (**62**).[155]



[60]

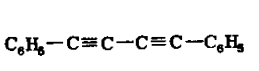


[61]

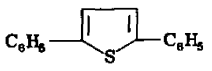


[62]

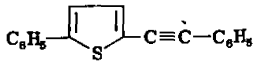
Schulte *et al.*[156] obtained thiophenes in 60–80% yield by saturating an alkaline alcoholic solution of diphenylpolyines with H_2S. 1,4-Diphenylbutadiyne (**63**) gave 2,5-diphenylthiophene (**64**) and 1,6-diphenylhexatriene gave (**65**). It is interesting to note that 1,8-diphenyloctatetrayne gave only (**66**) and no bithienyl derivative.



[63]



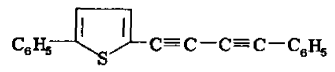
[64]



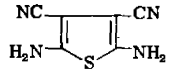
[65]

[155] F. Ya. Perveev and N. Y. Kudryashova, *Zhur. Obshchei Khim.* **23**, 1569 (1953); *Chem. Abstr.* **48**, 10727 (1954).

[156] K. E. Schulte, J. Reisch, and L. Hörner, *Angew. Chem.* **72**, 920 (1960).



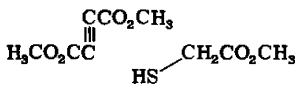
[66]



[67]

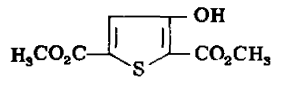
The ease with which 2,5-diamino-3,4-dicyanothiophene (**67**) is formed in 92% yield by saturating a solution of tetracyanoethylene in acetone–carbon disulfide with H_2S is reminiscent of the aforementioned reactions.[157]

Another elegant route to thiophene compounds has, during recent years, been worked out by Fiesselmann *et al.*[158–163] In principle this synthesis consists of the reaction of methyl thioglycolate with acetylenic compounds, β-ketoesters or α,β-dihalocarboxylates, followed by a Dieckmann-type cyclization of the adduct, which in some cases proceeds so easily that aqueous alkali can be used.[161] In most cases sodium methylate in benzene or ether is used.[158,159] Thus dimethyl acetylenedicarboxylate (**68**) and methyl thioglycolate (**69**) give with sodium methylate in benzene[158] or, better, with alcoholic or aqueous sodium hydroxide,[161] 3-hydroxy-2,5-dicarbomethoxythiophene (**70**) in high yield. The structure of the intermediate addition product, when

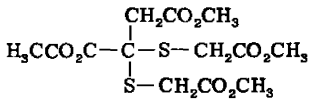


[68]

[69]



[70]



[71]

piperidine is used as a catalyst, has been identified as the thioacetal

[157] W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.* **80**, 2822 (1958).

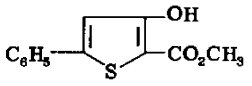
[158] H. Fiesselmann and P. Schipprack, *Chem. Ber.* **87**, 835 (1954).

[159] H. Fiesselmann, P. Schipprack, and L. Zeitler, *Chem. Ber.* **87**, 841 (1954).

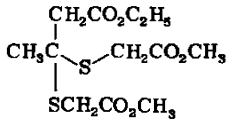
[160] H. Fiesselmann and G. Pfeiffer, *Chem. Ber.* **87**, 848 (1954).

[161] H. Fiesselmann and P. Schipprak, *Chem. Ber.* **89**, 1897 (1956).

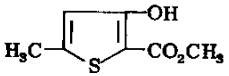
between methyl thioglycolate and methyl methoxalyl acetate (**71**) which can be used instead of (**68**) in this reaction.[162] It is claimed in a recent patent that dimethyl-α-β-dibromosuccinate can be used in the preparation of (**70**).[164] From ethyl propiolate and from ethyl phenylpropiolate, 3-hydroxy-2-carbomethoxy- and 3-hydroxy-2-carbomethoxy-5-phenyl-thiophene (**72**) have been obtained.[159] For a discussion on the tautomeric nature of these and other hydroxythiophenes, see Section VI,B,1.



[*72*]



[*73*]



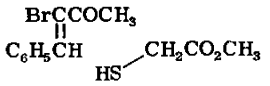
[*74*]

The mercaptals obtained by the acid catalyzed reaction of β-ketoesters, e.g., ethyl acetoacetate, with methyl thioglycolate (**73**) undergo the Dieckmann cyclization with alcoholic potassium hydroxide at lower temperatures to give ethyl 3-hydroxy-5-methyl-2-thiophenecarboxylate (**74**) in 75% yield.[160,163] Besides ethyl acetoacetate, ethyl α-ethylacetoacetate, ethyl benzoyl acetate, and ethyl cyclopentanonecarboxylate were also used in this reaction.[163] It is claimed that β-diketones, hydroxy- or alkoxy-methyleneketones, or β-ketoaldehyde acetals also can be used in this reaction.[165] From acetylacetone and thioglycolic acid, 3,5-dimethyl-2-thiophenecarboxylic acid is obtained.[165]

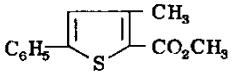
Other methods for the preparation of substituted thiophenecarboxylates have recently been announced by Fiesselmann. α- or β-

[162] H. Fiesselmann and W. Böhm, *Chem. Ber.* **89**, 1902 (1956).
[163] H. Fiesselmann and F. Thoma, *Chem. Ber.* **89**, 1907 (1956).
[164] H. Fiesselmann, German Patent 1020641; *Chem. Abstr.* **54**, 2357 (1960).
[165] H. Fiesselmann, *Angew. Chem.* **72**, 573 (1960).

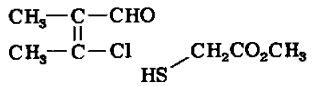
Halogenated-α,β-unsaturated ketones or aldehydes are reacted with methyl thioglycolate and cyclized with alkali alcoholate.[165] Thus β-bromobenzalacetone (**75**) gives methyl 3-methyl-5-phenyl-2-thiophenecarboxylate (**76**) and from α-methyl-β-chlorocrotonaldehyde (**77**), 4,5-dimethyl-2-thiophenecarboxylate (**78**) is obtained.



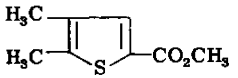
[*75*]



[*76*]

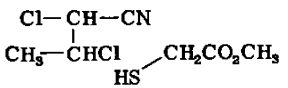


[*77*]

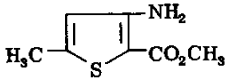


[*78*]

Using α,β-dihalogenonitriles instead of carbonyl derivatives in the reaction with methyl thioglycolate leads to methyl 3-amino-2-thiophenecarboxylates. Thus, α,β-dichlorobutyronitrile (**79**) gave methyl 3-amino-5-methyl-2-thiophenecarboxylate (**80**).[166]



[*79*]



[*80*]

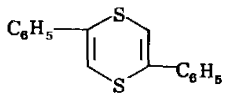
A review of earlier work on the synthesis of thiophenes through ring closure has appeared in *Organic Reactions*.[167]

B. From Other Heterocyclic Systems

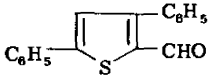
The rearrangement of arylsubstituted 1,4-dithiadienes, obtained from the Buntes salts derived from phenacyl halides,[168–171] offers a

[166] H. Fiesselmann, *Angew. Chem.* **71**, 377 (1959).
[167] D. E. Wolf and K. Folkers, *Org. Reactions* **6**, 410 (1951).
[168] W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.* **76**, 4960 (1954).

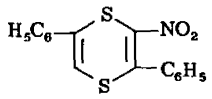
new route to 2,4-diarylsubstituted thiophenes. Thus 2,5-diphenyl-1,4-dithiadiene (**81**) gives 2,4-diphenylthiophene in 68% yield on thermal decomposition, and in 33% upon oxidation with hydrogen peroxide in acetic acid.[168] The oxidation does not proceed via the sulfones—these



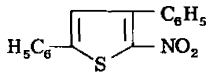
[*81*]



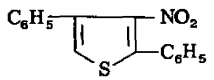
[*82*]



[*83*]



[*84*]

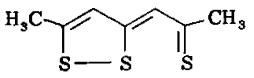


[*85*]

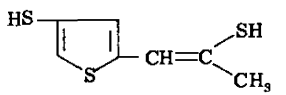
are stable compounds, the formation of which decreases the yield of thiophenes.[169] Rearrangement to a thiophene derivative also occurred during attempted Vilsmeier formylation of (**81**) leading to 3,5-diphenyl-2-thiophenealdehyde (**82**).[168] Different products are sometimes obtained with different procedures. Although the thermal decomposition of 2,5-diphenyl-3-nitro-1,4-dithiadiene (**83**), obtained upon nitration of (**81**), gives 20% 2-nitro-3,5-diphenylthiophene (**84**) and 11% of an unknown compound, the oxidation with H_2O_2 gives 31% of (**84**) and 46% 3-nitro-2,4-diphenylthiophene (**85**).[170] Although symmetrically substituted 1,4-dithiadienes give thiophenes in good yields, the preparative value of unsymmetrically substituted 1,4-dithiadienes is lowered owing to the formation, in most cases, of mixtures of isomeric thiophenes.[169,171] 1,4-Dithiadiene[172] and alkylsubstituted 1,4-dithiadienes[173] do not give thiophenes.

[169] W. E. Parham, I. Nicholson, and V. J. Traynelis, *J. Am. Chem. Soc.* **78**, 850 (1956).
[170] W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.* **77**, 68 (1955).
[171] W. E. Parham, E. T. Harper, and R. S. Berger, *J. Am. Chem. Soc.* **82**, 4932 (1960).
[172] W. E. Parham, B. Gadsby, and R. A. Mikulec, *J. Org. Chem.* **24**, 1819 (1959).
[173] W. E. Parham, G. L. O. Mayo, and B. Gadsby, *J. Am. Chem. Soc.* **81**, 5993 (1959).

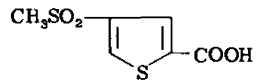
It now seems definitely proved that the thiothiophthene (**86**)[174] rearranged reversibly to a thiophene (**87**) under the influence of alkali and not to a thiepin derivative.[175] The dimethyl ether of (**87**) has been oxidized to 4-methylsulfonyl-2-thiophenecarboxylic acid (**88**).[175]



[*86*]

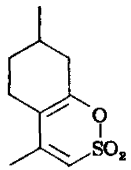


[*87*]

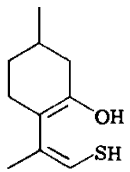


[*88*]

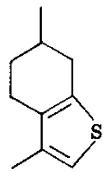
Thiophenes can be prepared from the sultones of α,β-unsaturated ketones. From the δ-sultone of pulegone (**89**), the thiophene (**91**) has been obtained through reduction with $LiAlH_4$ to (**90**), followed by dehydration of the latter.[176]



[*89*]



[*90*]

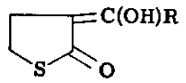


[*91*]

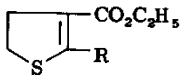
[174] F. Arndt and G. Traverso, *Chem. Ber.* **89**, 124 (1956).
[175] F. Arndt and W. Walter, *Chem. Ber.* **94**, 1757 (1961).
[176] W. Treibs, *Ann. Chem. Liebigs* **630**, 120 (1960).

2,4-Dichlorothiophene has become easily available through chlorination and dehydrochlorination of tetrahydrothiophene.[177,178] Another example of the aromatization of tetrahydrothiophene derivatives is the preparation of 3-substituted thiophenes by the reaction of 3-ketotetrahydrothiophene with Grignard reagents followed by the aromatization of the intermediate dihydrothiophene.[179] Recent gas chromatographic analysis[179a] showed, however, that 2,3-dichlorothiophene is the main product from the dehydrochlorination of tetrachlorotetrahydrothiophene.

Therefore, it may also be possible to aromatize the dihydrothiophene derivatives (**93**) obtained through the acid catalyzed rearrangement of α-hydroxymethylene-γ-thiobutyrolactone derivatives (**92**) in ethanol.[180]



[*92*]



[*93*]

The ease of formation of the thiophene ring is also evident from the fruitless attempts to prepare 3,4-dimethylene tetrahydrothiophene,[181,182] which only lead to the formation of 3,4-dimethylthiophene.

C. 2-Substituted Compounds

Most 2-substituted thiophenes are easily available through direct aromatic substitution, followed by suitable transformations of the groups so introduced. Some recent developments will be briefly outlined in this section.

[177] F. Runge, E. Profft, and R. Drux, *J. prakt. Chem.* **274**, 279 (1955).
[178] E. Profft and H. Wolff, *Ann. Chem. Liebigs* **628**, 96 (1959).
[179] H. Wynberg, A. Logothetis, and D. VerPloeg, *J. Am. Chem. Soc.* **79**, 1972 (1957).
[179a] E. Profft and G. Solf, *Ann. Chem. Liebigs* **649**, 100 (1961).
[180] F. Korte and K. H. Löhmer, *Chem. Ber.* **90**, 1290 (1957).
[181] C. S. Marvel and E. E. Ryder, Jr., *J. Am. Chem. Soc.* **77**, 66 (1955).
[182] C. S. Marvel, R. M. Novak, and J. Economy, *J. Am. Chem. Soc.* **78**, 6171 (1956).

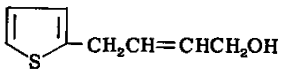
Procedures have been worked out which increased the yield of 2-bromothiophene to 78% on direct bromination in acetic acid–ether mixtures and to 67% in carbon tetrachloride.[134] With the mild brominating agent, dioxane dibromide, quantitative yields of 2-bromothiophene are obtained.[183] A very convenient procedure for the iodination of thiophenes consists of the acid-catalyzed (H_2SO_4) reaction with iodine and HIO_3, giving 2-iodothiophene in 75% yield.[184] In contrast to the HgO method, all the iodine is utilized.

As both 2-bromo- and 2-iodo-thiophene easily give Grignard reagents, they are of great importance in the preparation of other 2-substituted thiophenes. However, during recent years the Grignard reagent has been replaced with 2-thienyllithium which is obtained by direct metalation of thiophene with *n*-butyllithium[185] (cf. Section IV, B,2). 2-Thienylsodium prepared either from 2-chlorothiophene and sodium amalgam[186] or through transmetalation of thiophene with bromobenzene and sodium amalgam[186] has been used to only a small extent in the laboratory. The sodium compound gives a much lower yield than the magnesium or lithium compound in the reaction with epoxides[187] and aliphatic aldehydes,[188] whereas the aromatic aldehydes[188] give higher yields. Alkylation during the transmetalation can also be responsible for lower yields.[189] Finally, the increased experimental difficulties encountered in some cases make the use of thienylsodium less attractive, except when the use of Grignard reagents and sodium derivatives lead to different products, as in the reaction with butadiene monoxide.[190] With 2-thiophenemagnesium bromide, 1,4-addition leads to 4-(2-thienyl)buten-2-ol-1 (**94**), whereas thienylsodium yields 1-(2-thienyl)buten-3-ol-2 (**95**) via 1,2-addition to the epoxide ring.[190]

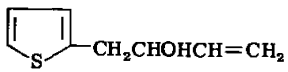
2-Thiocyanothiophene has been prepared through the reaction of

[183] A. P. Terent'ev, L. I. Bel'enkii, and L. A. Yanovskaya, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **24**, 1251 (1954).
[184] H. O. Wirth, O. Königstein, and W. Kern, *Ann. Chem. Liebigs* **634**, 84 (1960).
[185] H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.* **71**, 1870 (1949).
[186] J. W. Schick and H. D. Hartough, *J. Am. Chem. Soc.* **70**, 286 (1948).
[187] G. Van Zyl, J. F. Zack, Jr., E. S. Huyser, and P. L. Cook, *J. Am. Chem. Soc.* **76**, 707 (1954).
[188] G. Van Zyl, R. J. Langenberg, H. H. Tan, and R. N. Schut, *J. Am. Chem. Soc.* **78**, 1955 (1956).
[189] J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.* **74**, 1848 (1952).
[190] G. T. Gmitter and F. L. Benton, *J. Am. Chem. Soc.* **72**, 4586 (1950).

2-chloromercurythiophene with thiocyanogen,[191] but is most conveniently obtained by the $AlCl_3$ catalyzed reaction of thiophene with thiocyanogen.[192]



[94]



[95]

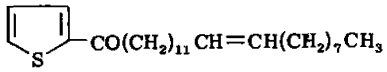
Nitration of thiophene with cupric nitrate in acetic anhydride or acetic acid[193] is considered to be milder than nitric acid in the same solvents and has been used successfully with thiophene derivatives which decomposed on conventional nitration.[194]

Sulfonation with sulfur trioxide, pyridine sulfur trioxide, pyridine bis-sulfur trioxide, and dioxane sulfur trioxide, which are useful sulfonating agents for acidophobic substances, have been applied to the thiophene series.[195] At room temperature the 2-monosulfonic acid (isolated as the barium salt) is obtained in 86% yield. Higher temperatures lead to a disulfonic acid.[195] However, sulfonation with chlorosulfonic acid appears to be more convenient,[196-198] as the sulfonyl chloride obtained can be used directly for the preparation of derivatives.

The introduction of the cheap and commercially available *N,N*-dimethylformamide, instead of *N*-methylformanilide in the $POCl_3$ catalyzed Vilsmeier formylation of thiophene,[199] has made 2-thiophenealdehyde one of the most important intermediates for the preparation of a variety of thiophene derivatives (cf. Section VI,D). This method is much more convenient than the Sommelet reaction with 2-thenyl chloride.[200]

[191] E. Cherbuliez and C. Giddey, *Helv. Chim. Acta* **35**, 160 (1952).
[192] E. Söderbäck, *Acta Chem. Scand.* **8**, 1851 (1954).
[193] N. I. Puthokin, *Sbornik Nauch. Trudov, Kuibyshev. Ind. Inst. im V. V. Kuibysheva* No. 5, p. 271 (1955); *Chem. Abstr.* **51**, 16419 (1957).
[194] V. N. Ivanova, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **28**, 1288 (1958).
[195] A. P. Terent'ev and G. M. Kadatskii, *Zhur. Obshchei Khim.* **22**, 153 (1952); *Chem. Abstr.* **46**, 11178 (1952).
[196] J. Cymerman-Craig, G. N. Vaughan, and W. K. Warburton, *J. Chem. Soc.* p. 4114 (1956).
[197] A. H. Blatt, S. Bach, and L. W. Kresch, *J. Org. Chem.* **22**, 1693 (1957).
[198] A. Buzas and J. Teste, *Bull. soc. chim. France* p. 793 (1960).
[199] E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.* **75**, 989 (1953).

Although the H_3PO_4 catalyzed acylation of thiophene[201] is the most convenient method for the acylation with acetic anhydride, the relative difficulty in obtaining higher aliphatic anhydrides has made the $SnCl_4$-catalyzed Friedel-Crafts reaction[202] with acid chlorides of primary importance in the preparation of 2-acylthiophenes. It has been used extensively in the preparation of long-chain aliphatic compounds through the use of ester acid chlorides of dicarboxylic acids (cf. Section VII,C). Stannic chloride is especially suitable as a catalyst for the acylation of unsaturated acids with acid chlorides, since, in contrast to aluminum chloride, it does not catalyze the addition of thiophene to the double bond. Thus erucic acid chloride gives 2-erucothienone (**96**).[203] However, the polymerizing effect of $AlCl_3$ on thiophene has apparently been somewhat overestimated, as a 90% yield of 2-acetylthiophene has been obtained in carbon disulfide.[204]



[96]

A very convenient method for the direct acylation of thiophenes with the free acids has been introduced by Yuryev. It consists of refluxing the acid with $SiCl_4$ in benzene, and without isolation of the formed tetraacyloxysilanes, $Si(OCOR)_4$, reacting them with $SnCl_4$ and thiophene.[205,206] The yields are between 57 and 94%. The lower

[200] K. B. Wiberg, *Org. Syntheses, Collective Vol.* **III**, 811 (1955).
[201] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.* **69**, 3093 (1947).
[202] G. Stadnikov and I. Goldfarb, *Ber. deut. chem. Ges.* **61**, 2341 (1928).
[203] N. P. Buu-Hoi, N. D. Xuong, and E. Lescot, *J. Org. Chem.* **21**, 621 (1956).
[204] N. P. Buu-Hoi and N. Hoan, *Rec. trav. chim.* **68**, 5 (1949).
[205] Yu. K. Yur'ev and G. B. Elyakov, *Proc. Acad. Sci. U.S.S.R. Sect. Chem.* (*Eng. Transl.*) **86**, 377 (1952).
[206] Yu. K. Yur'ev, G. B. Elyakov, N. S. Zefirov, and A. N. Vysokosof, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **26**, 3717 (1956).

yields are obtained with sterically hindered acids, e.g., trimethylacetic acid, and also with long-chain fatty acids.[206] Palmitic acid thus gave 60% pentadecyl 2-thienylketone, whereas cyclopentane- and cyclohexane-carboxylic acids gave 80% yields of the corresponding ketones.[206] Unsaturated ketones have also been prepared in this way from acids such as vinylacetic, 4-pentenoic, and 3-cyclohexenecarboxylic.[207] The yields are, however, only 20–30%. $ZnCl_2$, $BeCl_2$, BF_3, and $TiCl_4$ can also be used as catalysts in the acylation of thiophenes with tetraacyloxysilanes, $TiCl_4$ giving especially high yields.[208] Triacyloxyboranes (from carboxylic acids and BBr_3) also acylate thiophene, but tetraacetoxygermanes (from $GeCl_4$ and carboxylic acids) are unreactive.[209] It appears that the Yuryev procedure is more convenient than the P_2O_5 method which has been used earlier for the "direct" acylation of thiophenes with carboxylic acids.

Although a variety of methods can thus be used for the acylation of thiophene, the alkylation of thiophene is not so easily performed as polymerization often occurs. Moreover, the H_2SO_4 catalyzed alkylation of thiophene with isobutylene or propylene gives a mixture of about equal amounts of the 2- and 3-isomers.[210] The proportion of 2-isomer increases when thiophene is alkylated with *t*-butyl chloride using $SnCl_4$,[211] $AlCl_3$,[212] or $FeCl_3$[213] as a catalyst, the proportion of 2-isomer to 3-isomer being about 3:1. Isomer-free 2-*t*-butylthiophene has been obtained by the reaction of 2-thiophenemagnesium bromide with *t*-butyl bromide.[212] β-Chlorovinylketones condense with thiophene in the presence of $SnCl_4$. Through such a condensation β-chlorovinyl methyl ketone gave 2-thenylideneacetone in 39% yield.[214]

Alkylsubstituted thiophenes are, however, easily prepared from the

[207] Yu. K. Yur'ev, G. B. Elyakov, and I. M. Milshtein, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **26**, 3559 (1956).

[208] Yu. K. Yur'ev, Z. V. Belyakova, and N. S. Zefiróv, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **27**, 3299 (1957).

[209] Yu. K. Yur'ev, Z. V. Belyakova, P. V. Kostetskii, A. I. Prokofyev, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **30**, 415 (1960).

[210] H. D. Hartough, "Thiophene and Its Derivatives," p. 497. Interscience, New York, 1952.

[211] M. Sy, N. P. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.* p. 1975 (1954).

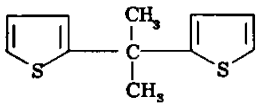
[212] P. Cagniant and D. Cagniant, *Bull. Soc. chim. France* p. 1152 (1956).

[213] Ya. L. Goldfarb and I. S. Korsakova, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 481 (1954).

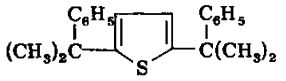
[214] A. N. Nesmeyanov, N. K. Kochetkov, and L. A. Matov, *Doklady Akad. Nauk SSSR.* **92**, 85 (1953); *Chem. Abstr.* **48**, 10665 (1954).

acylated compounds through Clemmensen reduction and especially through the Huang-Minlon modification of the Wolff-Kishner reduction (cf. Section VI,D).

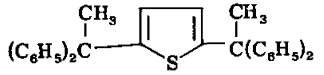
The condensation of thiophene with ketones, under the influence of 70% H_2SO_4, leads to di-2-thienylmethane derivatives. With acetone, 2,2-di-(2-thienyl)propane (**97**) is obtained.[215] The condensation of thiophene with dimethyl phenyl carbinol, methyl diphenyl carbinol, and *t*-butylalcohol, in the presence of $SnCl_4$ gave (**98**), (**99**), and 2,5-di-*t*-butylthiophene, respectively.[216] Triphenyl carbinol does not



[*97*]



[*98*]



[*99*]

react with thiophene.

The chloromethylation of thiophene has come somewhat into discredit, partly because of the lachrymatory nature of 2-thenyl chloride, partly because this reaction is highly dependent on the conditions used. Formalin in concentrated hydrochloric acid has been used[217] for chloromethylation, as has the anhydrous system, formaldehyde and hydrogen chloride.[111] The use of α-chloromethyl methylether has also been recommended.[218] The sensitivity of chloromethylation to the experimental conditions is illustrated by the fact that addition of zinc chloride gives di-(2-thienyl)methane as the main product and

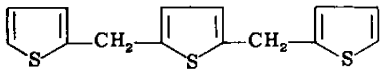
[215] J. W. Schick and D. J. Crowley, *J. Am. Chem. Soc.* **73**, 1377 (1951).

[216] Ya. L. Goldfarb and I. S. Korsakova, *Proc. Acad. Sci. USSR. Sect. Chem.* (*Eng. Transl.*) **96**, 283 (1954).

[217] K. B. Wiberg and H. F. McShane, *Org. Syntheses, Collective Vol.* **III**, 197 (1955).

[218] P. Cagniant, *Bull. soc. chim. France* p. 847 (1949).

2,5-di(2-thenyl)thiophene (**100**) as a by-product.[219] In spite of these difficulties, 2-thenyl chloride has been used for the preparation of many thiophene derivatives through the utilization of its very reactive halogen (cf. Section VI,C).



[*100*]

Thiophene has been thiocyanomethylated to a mixture of 2-thenylthiocyanate and 2-thenylisothiocyanate in 20% yield by the use of sodium thiocyanate, formalin, and dilute sulfuric acid.[220]

The effects of substituents in the thiophene nucleus on the reactions discussed in the foregoing and on other substitution reactions will be given in Sections IV and V. The reactivity of the functional groups will be discussed in Section VI.

D. 3-Substituted Compounds

Until recently, 3-substituted thiophenes have been rare and difficultly available compounds, as they, with very few exceptions, cannot be prepared by direct substitution of thiophene.

Campaigne *et al.* have used 3-thenyl bromide obtained by benzoyl peroxide-catalyzed, side-chain bromination of 3-methylthiophene with *N*-bromosuccinimide, as a starting material for 3-substituted thiophenes.[221,222] 3-Methylthiophene is now prepared commercially from itaconic acid. The reactive halogen in 3-thenyl bromide could be directly reacted with a variety of nucleophiles, such as cyanide,[223] or malonate,[223,224] to give more complex 3-substituted compounds. 3-Thenyl bromide was converted by the Sommelet reaction to 3-thiophenealdehyde[221,225] which, with silver oxide, was oxidized to 3-thiophenecarboxylic acid.[221,226] These compounds were then used for the preparation of 3-substituted compounds of pharmacological interest.[227-229] It is, of course, obvious that only compounds containing a carbon—carbon bond in the 3-position can be prepared by this method.

[219] Ya. L. Goldfarb and Y. L. Danyushevskii, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 1395 (1956).
[220] Y. Matsuki and T. Sone, *Kôgyô Kagaku Zasshi* **63**, 2173 (1960).
[221] E. Campaigne and W. M. LeSuer, *J. Am. Chem. Soc.* **70**, 1555 (1948).
[222] E. Campaigne and B. F. Tullar, *Org. Syntheses* **33**, 96 (1953).
[223] E. Campaigne and W. C. McCarthy, *J. Am. Chem. Soc.* **76**, 4466 (1954).
[224] S. Gronowitz, *Arkiv Kemi* **6**, 283 (1953).
[225] E. Campaigne, R. C. Bourgeois, and W. C. McCarthy, *Org. Syntheses* **33**, 93 (1953).

The other starting material for the preparation of 3-substituted thiophenes, which has been extensively used by the present author, is 3-bromothiophene. This compound was first prepared by the removal of the α-halogens of 2,3,5-tribromothiophene[61] (which is easily prepared by the direct bromination of thiophene[230]) through hydrolyses of the Grignard reagent prepared in the presence of large amounts of ethyl bromide (entrainment method). A 50% yield of 3-bromothiophene was obtained when 5 moles of ethyl bromide was used.[61] However, a much more convenient method has recently been found consisting of the dehalogenation of 2,3,5-tribromothiophene with zinc dust in acetic acid, which gives 3-bromothiophene in 80–90% yield.[231] The preparations of 3-bromothiophene by removal of the α-halogens of 2,3,5-tribromothiophene with *n*-butyllithium and water,[232] and through simultaneous debromination and decarboxylation of 4,5-dibromo-2-thiophenecarboxylic acids with copper and quinoline, are inferior.[233]

3-Methoxythiophene[63] and 3-cyanothiophene[233] have been prepared from 3-bromothiophene by means of a cupric oxide-catalyzed Williamson synthesis and by reaction with cuprous cyanide in quinoline, respectively.

The usefulness of the Grignard reagent of 3-bromothiophene is somewhat limited as it can only be prepared by the entrainment method.[61] The simultaneous formation of Grignard reagents from 3-bromothiophene and a fivefold molar excess of ethyl bromide gave, however, a 55% yield of 3-thiophenecarboxylic acid upon carbonation.[61] With acetaldehyde, a 55% yield of methyl 3-thienyl carbinol

[226] E. Campaigne and W. LeSuer, *Org. Syntheses* **33**, 94 (1953).
[227] E. Campaigne and W. LeSuer, *J. Am. Chem. Soc.* **70**, 3498 (1948).
[228] E. Campaigne and R. C. Bourgeois, *J. Am. Chem. Soc.* **75**, 2702 (1953).
[229] E. Campaigne and R. L. Patrick, *J. Am. Chem. Soc.* **77**, 5425 (1955).
[230] C. Troyanowsky, *Bull. soc. chim. France* p. 424 (1955).
[231] S. Gronowitz, *Acta Chem. Scand.* **13**, 1045 (1959).
[232] S. O. Lawesson, *Arkiv Kemi* **11**, 373 (1957).
[233] S. Nishimura, R. Motoyama, and E. Imoto, *Bull. Univ. Osaka Prefect. Ser.A.* **6**, 127 (1958).

was obtained[230] and with ethyl cyanide, a low yield of ethyl 3-thienyl ketone has been obtained.[234]

Through halogen–metal interconversion between 3-bromothiophene and *n*-butyllithium at −70°C, 3-thienyllithium could be prepared, which at this temperature is stable enough to be chosen as the reagent for the preparation of 3-substituted thiophenes.[235] 3-Thiophenecarboxylic acid was obtained in 80% yield upon reaction with carbon dioxide.[235] 3-Thiophenealdehyde and 2-(3-thienyl)ethanol were prepared through the reaction of 3-thienyllithium with *N,N*-dimethylformamide and ethylene oxide, respectively.[236] Thienylsubstituted secondary alcohols were obtained through the reaction of 3-thienyllithium with aromatic or aliphatic aldehydes.[237] These alcohols could be oxidized to the corresponding ketones with chromic oxide in acetic acid.[237] 3-Thienylsubstituted ketones have also been prepared by the reaction of 3-thenoyl chloride with organocadmium compounds,[238] by the Friedel-Crafts reaction of 3-thenoyl chloride with thiophene,[238] and by the reaction of 3-thienyllithium with benzonitrile.[237] Dimethyl disulfide has been reacted with 3-thienyllithium to give methyl 3-thienyl sulfide in 85% yield.[43] The 3-thienyllithium reagent has been used for the preparation of 3-thienylsulfinic acid,[43] 3-thienylboronic acid,[239] and 3-deuterothiophene[240] through the reactions with sulfur dioxide, *n*-butyl borate, and deuteroacetic acid, respectively. 3-Iodothiophene is prepared more conveniently by the reaction of 3-thienyllithium with iodine[64] than by removal of three iodine atoms from tetraiodothiophene with aluminum amalgam.[241] The reaction with sulfur gives a 65% yield of 3-thiophenethiol,[64] and with phenyl thiocyanate, a 44% yield of phenyl 3-thienyl sulfide was obtained.[242] 3,3′-Bithienyl has become easily available through the coupling of 3-thienyllithium with cupric chloride.[243] It has also been prepared through the reaction of 3-thienyllithium with 3-ketotetrahydrothiophene followed by dehydration and aromatization of the intermediate tertiary alcohol.[243] The reaction of 3-ketotetrahydrothiophene with

[234] J. Hoch, *Compt. rend. acad. sci.* **234**, 1981 (1952).
[235] S. Gronowitz, *Arkiv Kemi* **7**, 361 (1954).
[236] S. Gronowitz, *Arkiv Kemi* **8**, 441 (1955).
[237] S. Gronowitz, *Arkiv Kemi* **12**, 533 (1958).
[238] E. Campaigne and H. L. Thomas, *J. Am. Chem. Soc.* **77**, 5365 (1955).
[239] S. O. Lawesson, *Arkiv Kemi* **11**, 387 (1957).
[240] S. Gronowitz, P. Moses, and R. Håkansson, *Arkiv Kemi* **16**, 267 (1960).
[241] I. J. Rinkes, *Rec. trav. chim.* **53**, 643 (1934).
[242] S. Gronowitz and R. Håkansson, *Arkiv Kemi* **17**, 73 (1960).
[243] S. Gronowitz and H.-O. Karlsson, *Arkiv Kemi* **17**, 89 (1960).

Grignard reagents has been introduced by Wynberg *et al.*[179] for the preparation of 3-substituted thiophenes.

By reaction of 3-thienyllithium with magnesium bromide, the Grignard reagent, free from entrainment Grignard reagent, was obtained,[237] which is useful for the preparation of 3-acetothiophene by reaction with acetic anhydride at −70°C[237] and for the preparation of 3-*t*-butoxythiophene through reaction with *t*-butyl perbenzoate.[244] It is the opinion of the present author that most 3-substituted thiophenes are prepared more conveniently from 3-thienyllithium than from 3-thenyl bromide. The latter method, however, is superior if the introduction of the 3-thenyl group is desired.

2,5-Dichlorothiophene can also be used for the synthesis of 3-substituted thiophenes, since it can be smoothly acylated[245] and chloromethylated[236] in the 3-position, and the halogens can then be readily removed at the appropriate stage. 3-Thenylsuccinic acid (**28**) has thus been obtained by treating 2,5-dichloro-3-thenylsuccinic acid with sodium amalgam.[236] 2-Bromo-3-thenylbromide can be utilized in a similar way.[236]

Finally, certain 3-substituted compounds can be prepared by utilizing the 4-(*meta*) directing power (cf. Section IV,B) of some groups in the 2-position which afterward can be removed. 3-Nitrothiophene is prepared by nitration of 2-thiophenesulfonyl chloride and by removal of the sulfonic acid group of the 4-nitro-2-sulfonyl chloride formed with superheated steam.[197] Another approach to 3-nitrothiophene is to nitrate 2-cyanothiophene, separate the 4-nitro-2-cyanothiophene from the 5-isomer, hydrolyze, and decarboxylate.[246] A final method of preparation of 3-nitrothiophene is by simultaneous debromination and decarboxylation of 5-bromo-4-nitro-2-thiophenecarboxylic acid obtained through the nitration of methyl 5-bromo-2-thiophenecarboxylate.[247]

IV. Electrophilic Aromatic Substitution

A. Comparison of the 2- and 3-Positions of Thiophene with Benzene

Since the time of the classic investigations, it has been well known

[241] S. Gronowitz, *Arkiv Kemi* **16**, 363 (1960).
[245] J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.* **73**, 2779 (1951).
[246] P. Reynaud and R. Delaby, *Bull. soc. chim. France* p. 1614 (1955).
[247] R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi* **78**, 950 (1957); *Chem. Abstr.* **54**, 14223 (1960).

that thiophene reacted with electrophilic reagents much more easily and rapidly than benzene. It can, for instance, be brominated, acylated, formylated, chloromethylated, and mercurated under conditions under which benzene does not react.[3] It is also well known that substitution takes place with very few exceptions, predominantly, if not exclusively, in the 2-position.

Only within the past few years have serious attempts been made to estimate quantitatively the differences in reactivity between thiophene and benzene and between the 2- and 3-position of thiophene. Careful investigation on the acid-induced exchange of deuterium[248] and tritium[248,249] have shown that the ratios of the exchange rates in the 2- and 3-positions are 1045 ± 61 for deuterium and 911 ± 60 for tritium in 57% by weight aqueous sulfuric acid at 24.6°C. A kinetic isotope effect in the isotopic exchange has been found to be $k_T/k_D = 0.51 \pm 0.03$ in the 2-position and $k_T/k_D = 0.59 \pm 0.04$ in the 3-position.[248]

The acid cleavage of the aryl—silicon bond (desilylation), which provides a measure of the reactivity of the aromatic carbon of the bond, has been applied to 2- and 3-thienyl trimethylsilane.[250] It was found that the 2-isomer reacted only 43.5 times faster than the 3-isomer and 5000 times faster than the phenyl compound at 50.2°C in acetic acid containing aqueous sulfuric acid.[250] The results so far are consistent with the relative reactivities of thiophene upon detritiation if a linear free-energy relationship between the substituent effect in detritiation and desilylation is assumed, as the *p*-methyl group activates about 240[250] (200–300)[251] times in detritiation with aqueous sulfuric acid and about 18 times in desilylation.[250] A direct experimental comparison of the difference between benzene and thiophene in detritiation has not been carried out, but it may be mentioned that even in 80.7% sulfuric acid, benzene is detritiated about 600 times slower than 2-tritiothiophene. The aforementioned consideration makes it probable that under similar conditions the ratio of the rates of detritiation of thiophene and benzene is larger than in the desilylation. A still larger difference in reactivity between the 2-position of thiophene and benzene has been found for acetoxymercuration which

[248] B. Östman and S. Olsson, *Arkiv Kemi* **15**, 275 (1960).
[249] K. Halvarson and L. Melander, *Arkiv Kemi* **8**, 29 (1955).
[250] F. B. Deans and C. Eaborn, *J. Chem. Soc.* p. 2303 (1959).
[251] S. Olsson, *Arkiv Kemi* **16**, 489 (1961).

is claimed to be 97,000 times more rapid for thiophene than benzene.[252] On the other hand, in nitration, thiophene is said to be only 850 times as reactive as benzene.[252]

Through a study of the influence of thiophene and other aromatic compounds on the retardation and chain transfer on the polymerization of styrene by stannic chloride, the relative rates of attack of a carbonium-ion pair could be obtained.[253] It was found that thiophene in this reaction was about 100 times more reactive than *p*-xylene and somewhat less reactive than anisole.[253]

It is thus apparent that the selectivity of a reagent toward thiophene and benzene can differ appreciably, and this difference in selectivity is also strongly noticeable in the proportions of 2- and 3-isomers formed. Although in certain reactions no 3-isomer has been detected, appreciable amounts have been found in other reactions. Thus 0.3% of the 3-isomer has been found in the chlorination of thiophene.[254] Earlier results indicated that 5–10% 3-nitrothiophene is formed in the nitration of thiophene[197,255] and a recent gas-chromatographic analysis by Östman shows that the mononitrothiophene fraction contains as much as 15% of the 3-isomer. It appears that gas-chromatographic analysis should be very useful for the detection of small amounts of 3-isomers in other substitution reactions. However, from routine analyses of IR spectra, it appears to the present author that the amount of 3-isomers formed in acylation, formylation, and bromination of thiophene are certainly less than a few per cent.

As mentioned before, in the alkylation of thiophene the proportion of 2- to 3-isomer varies from 1:1 to 3:1, depending on the reagent and catalyst used.[211–213,256,257] The poor selectivity in the Friedel-Crafts alkylations are, of course, well known from the benzene series, where large proportions of the *meta* isomers are obtained upon alkylation of benzenes with *ortho-para* directing substituents.[258] H. C.

[252] R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi* **78**, 962 (1957); *Chem. Abstr.* **54**, 14224 (1960).
[253] C. G. Overberger and G. F. Endres, *J. Am. Chem. Soc.* **75**, 6349 (1953).
[254] H. L. Coonradt, H. D. Hartough, and G. C. Johnson, *J. Am. Chem. Soc.* **70**, 2564 (1948).
[255] W. Steinkopf and T. Höpner, *Ann. Chem. Liebigs* **501**, 174 (1933).
[256] W. G. Appleby, A. F. Sartor, S. H. Lee, and S. W. Kapranos, *J. Am. Chem. Soc.* **70**, 1552 (1948).
[257] W. M. Kutz and B. B. Corson, *J. Am. Chem. Soc.* **71**, 1503 (1949).
[258] A. W. Francis, *Chem. Revs.* **43**, 257 (1948).

Brown has proposed that the importance of *meta* substitution in the alkylation is related to the "activity" of the attacking species, and he utilized the relative reactivity of toluene and benzene in the reaction under consideration as a measure of this "activity."[259-261] It might be possible that the amounts of 3-isomer formed may similarly be related to the relative reactivity of thiophene and benzene in different reactions.

The reason for this difference in selectivity of different electrophilic reagents between the 2- and 3-positions must be sought in the finer details of the mechanism of electrophilic aromatic substitution; Melander and co-workers are studying this problem by means of isotope effects.

This difference in selectivity makes it necessary to consider both the substituent and the reagent when discussing the directing effects of substituents to a much larger extent than is necessary in the benzene series.

As has been mentioned before, the preferential α-substitution of thiophene is probably not related to excess negative charge at the α-carbon in the ground state but is best understood by considering the localization energies of the transition states for 2- and 3-substitution, respectively.[15,18]

B. Directing Effects of Substituents in Electrophilic Substitution

1. *General*

The modern electronic theory of organic chemistry was first systematically applied by the present author for discussing the directing effects of substituents in thiophene.[21] Although the directing effects of substituents and the isomeric distribution in electrophilic substitution are best discussed and understood in terms of the influence of the substituents on the energies of the transition states, the often simpler approach of considering their effect on the electron densities of the ground state was used (cf. Section II,A,2).[21]

Unfortunately only in a few cases have attempts been made to achieve quantitative analysis of isomer mixtures, and it is possible that in many cases when it is stated that only one isomer is formed,

[259] H. C. Brown and Nelson, K. LeRoy, *J. Am. Chem. Soc.* **75**, 6292 (1953).
[260] H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.* **77**, 2300 (1955).
[261] H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.* **77**, 2306 (1955).

minor amounts of other isomers may have been overlooked. In some cases the purity of the isomers obtained is doubtful. The tendency toward the formation of solid solutions in the thiophenes series and the occurrence of sharp melting eutectic mixtures makes the melting point unreliable as a criterion of purity. A striking example is the case of 4-nitro-2-thiophenealdehyde, where three different research groups described an eutectic mixture of 5- and 4-nitro-2-thiophenealdehyde[262-264] melting at 36–37°C as pure 4-nitro-2-thiophenealdehyde, which has a mp of 56°C.[265,266]

Correct structure proofs were earlier difficult to obtain, usually involving several reaction steps, and the structures were, therefore, assigned by analogy in many cases. However, through Raney nickel desulfurization (cf. Section VII,C), through NMR spectroscopy,[34,43,44,244] and through polarographic analysis[267] such problems are now easily solved.

2. *Directing Effects of $\pm I + M$-Substituents in the 2-Position*

With weakly directing $-I + M$-substituents such as the halogens, the α-directing power of the ring sulfur dominates and substitution appears to occur exclusively in the 5-position. 2-Chloro-, 2-bromo-, and 2-iodo-thiophene are sulfonated both with chlorosulfonic acid[198,268] and SO_3[269] in the 5-position. In the chlorination of chlorothiophene, 1% of 2,3-isomer has been detected,[254] but no 2,3-isomer has been found in the bromination of 2-bromothiophene.[232] It is claimed that 2-chlorothiophene is chloromethylated,[270] nitrated,[271] and formylated[272] in the 5-position. The necessity to obtain stringent structure proof is illustrated by the fact that the action of *t*-butyl chloride on 2-bromothiophene in the presence of $FeCl_3$ leads to 2,5-*t*-

[262] G. Gever, *J. Am. Chem. Soc.* **75**, 4585 (1953).
[263] W. O. Foye, J. J. Hefferren, and E. G. Feldmann, *J. Am. Chem. Soc.* **76**, 1378 (1954).
[264] N. P. Buu-Hoi and D. Lavit, *J. Chem. Soc.* p. 1721 (1958).
[265] G. Gever, *J. Am. Chem. Soc.* **77**, 577 (1955).
[266] J. Tirouflet and P. Fournari, *Compt. rend. acad. sci.* **243**, 61 (1956).
[267] J. Tirouflet and J. P. Chané, *Compt. rend. acad. sci.* **243**, 500 (1956).
[268] R. H. Cundiff and R. R. Estes, *J. Am. Chem. Soc.* **72**, 1424 (1950).
[269] A. P. Terent'ev and G. M. Kadatskii, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **21**, 1667 (1955); *Chem. Abstr.* **46**, 2536 (1952).
[270] N. A. Rosenthal, *J. Am. Chem. Soc.* **73**, 5902 (1951).
[271] A. L. Stone and R. R. Estes, *J. Am. Chem. Soc.* **74**, 2691 (1952).
[272] A. W. Weston and R. J. Michaels, *J. Am. Chem. Soc.* **72**, 1422 (1950).

butyl-3-bromothiophene,[273] and the sulfonation of 2,5-dibromothiophene with chlorosulfonic acid gives, at 110°C, 2,4-dibromo-3,5-thiophenedisulfonic acid.[198,273a]

If the activating effect of a $\pm I + M$-substituent (such as CH_3, $NHCOCH_3$, SCH_3, or OCH_3) were equal in the 3- and 5-positions, one would, of course, expect that substitution should occur in the 5-position because of the directing power of the sulfur. The experimental results show, however, that such substituents activate the 3-position much more than the 5-position. Thus the nitration of 2-methylthiophene leads to a mixture of about 70% 5-nitro- and 30% 3-nitro-2-methylthiophene.[34] Similarly, from the nitration of 2-methoxythiophene a 24% yield of the 3-nitro and a 36% yield of the 5-nitro isomers were isolated.[274] In the acylation of 2-methoxythiophene both isomers were also isolated, but in low total yield.[274]

This activation of the *ortho* position is most strikingly illustrated in the reactivity of 2,5-dimethylthiophene, which competitive experiments have shown to undergo the $SnCl_4$-catalyzed Friedel-Crafts reaction more rapidly than thiophene and even 2-methylthiophene.[275]

The influence of the reagent on the isomer distribution is evident from the fact that 2-methoxythiophene is formylated[276] and brominated[274] (with *N*-bromosuccinimide) only in the 5-position. Similarly, although 3-bromo-2-methylthiophene has been detected in the bromination of 2-methylthiophene with bromine,[277] only the 5-isomer (besides some side-chain bromination) is obtained in the bromination of alkylthiophenes with *N*-bromosuccinimide.[240,278] However, the mechanism of the latter type of bromination is not established. No lines attributable to 2-methyl-3-thiocyanothiophene or 2-methyl-3-chlorothiophene could be detected in the NMR spectra of the substitution products (5-isomers) obtained upon thiocyanation with thiocyanogen or chlorination with sulfuryl chloride.[38] 2-Methyl- and 2-ethyl-thiophene give, somewhat unexpectedly, upon alkylation with *t*-butyl chloride in the presence of $FeCl_3$, only 5-*t*-butyl monosubstituted and

[273] Ya. L. Goldfarb and I. S. Korsakova, *Doklady Akad. Nauk SSSR.* **89**, 301 (1953); *Chem. Abstr.* **48**, 7598 (1954).

[273a] Recent gas chromatographic analysis showed that about 9% of 2,3-dibromo- and 2% of 2,4-dibromothiophene is formed in the dibromination of thiophene.

[274] J. Sicé, *J. Am. Chem. Soc.* **75**, 3697 (1953).

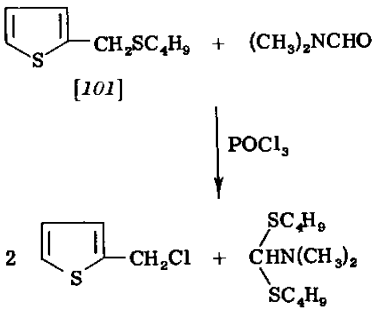
[275] Ya. L. Goldfarb, V. P. Litvinov, and V. I. Shvedov, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **30**, 555 (1960).

[276] E. Profft, *Ann. Chem. Liebigs* **622**, 196 (1959).

[277] W. Steinkopf, *Ann. Chem. Liebigs* **513**, 281 (1934).

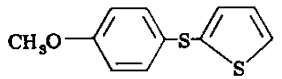
[278] P. Cagniant and D. Cagniant, *Bull. soc. chim. France* p. 713 (1952).

3,5-di-*t*-butyl disubstituted products.[213] Friedel-Crafts acylation of 2-ethylthiophene leads only to 5-acylsubstitution,[279] and only 5-substituted products have been isolated from the acylation (including formylation) and nitration of 2-*t*-butylthiophene.[211] Nitration of 2-thenyl chloride gives the 5-isomer.[280] The structure was proved by oxidation to 5-nitro-2-thiophenecarboxylic acid.[280] 2-Methylthiothiophene is formylated,[281] iodinated,[281] (HgO method) and nitrated[196] in the 5-position. Although 2-ethylthiothiophene is formylated normally in the 5-position by the use of *N*,*N*-dimethylformamide and $POCl_3$ to give 2-ethylthio-5-thiophenealdehyde,[282] a new reaction was discovered when formylation of the homologous 2-thenyl *n*-butyl sulfide (**101**) was attempted, yielding 2-chloromethylthiophene and a thioacetal of *N*,*N*-dimethylformamide (**102**).[283] In spite of the activating



[*101*] [*102*]

methoxy group in the benzene ring of 2-(*p*-methoxyphenylthio)thiophene (**103**), it is formylated in the thiophene ring yielding 5-(*p*-



[*103*]

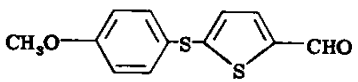
[279] N. P. Buu-Hoi, *J. Chem. Soc.* p. 2418 (1958).

[280] M. Bercot-Vatteroni, R. C. Moreau, and P. Reynaud, *Compt. rend. acad. sci.* **252**, 2419 (1961).

[281] J. Cymerman-Craig and J. W. Loder, *J. Chem. Soc.* p. 237 (1954).

[282] B. P. Fedorov and F. M. Stoyanovich, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 1705 (1960).

[283] B. P. Fedorov and F. M. Stoyanovich, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 1700 (1960).



[*104*]

methoxyphenylthio)-2-thiophenealdehyde (**104**).[284] The acylation of 2-alkylthiothiophenes also occurs in the 5-position.[285] Higher yields are obtained with H_3PO_4 and acetic anhydride than with $SnCl_4$ and acetyl chloride because of tar formation in the latter case. From the competitive acetylation of an equimolar mixture of thiophene and 2-methylthiothiophene with an insufficient amount of acetyl chloride, 15% 2-acetylthiophene and 48% 5-methylthio-2-acetylthiophene were isolated, demonstrating the activating effect of the SCH_3 group.[285] It should, perhaps, be pointed out that in these and in many of the experiments mentioned in the foregoing, no efforts were made to detect small amounts of other isomers.

The sulfonation of 2-acetamidomethylthiophene and of 2-acetamidothiophene attracted considerable interest in connection with work on potential thiophene chemotherapeutics, although from this point of view these investigations have given little reward. Sulfonation of 2-acetamidomethylthiophene with chlorosulfonic acid occurs in the 5-position.[286] At room temperature 100% sulfuric acid yields 80% 5-acetamido-2-thiophenesulfonic acid.[287,288] With chlorosulfonic acid sulfonation cannot be stopped at the monosubstitution stage and 2-acetamido-3,5-thiophene disulfonyl chloride is obtained.[198,289,290] In recent Russian work the isolation of a monosulfonated product is claimed, however.[291] With the activating +M-substituents, disubstitution, which is easily achieved, always leads exclusively to 3,5-disub-

[284] B. P. Fedorov and F. M. Stoyanovich, *Zhur. Obshchei Khim.* **31**, 238 (1961); *Chem. Abstr.* **55**, 25908 (1961).
[285] Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *J. Gen. Chem. USSR. (Eng. Transl.)* **29**, 2003 (1959).
[286] J. Cymerman and D. F. Faiers, *J. Chem. Soc.* p. 165 (1952).
[287] C. D. Hurd and H. M. Priestley, *J. Am. Chem. Soc.* **69**, 859 (1947).
[288] H. Schreibler, E. Keintzel, and K. Falk, *Chem. Ber.* **87**, 1184 (1954).
[289] H. Y. Lew and C. R. Noller, *J. Am. Chem. Soc.* **72**, 5715 (1950).
[290] C. D. Hurd and J. Moffat, *J. Am. Chem. Soc.* **73**, 613 (1951).
[291] N. I. Putohkin and V. I. Yakovlev, *Sbornik Nauch. Trudov, Kuibyshev. Ind. Inst. im V. V. Kuibysheva* No. 5, p. 254 (1955); *Chem. Abstr.* **51**, 16420 (1957).

stitution. 2-Acetamidothiophene is formylated in the 5-position.[199,292,293] The structure was proved by reductive acetylation of 5-nitro-2-thiophenealdehyde diacetate with iron and acetic anhydride in acetic acid.[293]

The confusion which arose in connection with the structure of 5-acetylamino- and 4-acetylamino-2-thiophenecarboxylic acid has been resolved by Goldfarb *et al.*[294] The acid, mp 272–273°C, which Steinkopf and Müller[295] described as 4-acetylamino-2-thiophenecarboxylic acid and which they prepared by reduction and acetylation of 4-nitro-2-thiophenecarboxylic acid, was without comment tabulated by Hartough[296] as 5-acetylamino-2-thiophenecarboxylic acid. Since Campaigne and Archer[199] claimed that oxidation of 5-acetylamino-2-thiophenealdehyde gave the acid mp 272–273°C, Cymerman-Craig *et al.* concluded, after proving the structure of 5-acetylamino-2-thiophenealdehyde, that the acid mp 272–273°C was, in fact, the 5-isomer.[293] However, Goldfarb *et al.*[294] claim that Campaigne and Archer,[199] owing to very unfortunate coincidences, had mistaken acid potassium tartrate for the acetylamino acid. Goldfarb *et al.* prepared authentic 5-acetylamino-2-thiophenecarboxylic acid, mp 230–232°C (methyl ester, mp 171–171.5°C; ethyl ester, mp 161°C), through reduction of 5-nitro-2-thiophenecarboxylic acid with Raney nickel in acetic anhydride and proved the structure by Raney nickel desulfurization to δ-aminovaleric acid.[294] They also confirmed that the acid mp 272–273°C (methyl ester, mp 135–136°C; ethyl ester, mp 116–117°C) is 4-acetylamino-2-thiophenecarboxylic acid as originally stated by Steinkopf and Müller.[295] The statement of Tirouflet and Chané[297] that the acid obtained upon reduction and acetylation of 5-nitro-2-thiophenecarboxylic acid melts at 272°C must result from some mistake as they give the correct melting point for the methyl ester.

The nitration of 2-phenylthiophene gives two isomeric 2-phenylnitrothiophenes the structures of which have not been proved.[194]

[292] J. Cymerman-Craig and D. Willis, *Chem. & Ind. (London)* p. 797 (1953).
[293] J. Cymerman-Craig and D. Willis, *J. Chem. Soc.* p. 1071 (1955).
[294] Ya. L. Goldfarb, M. M. Polonskaya, B. P. Fabrichnyi, and I. F. Shalavina, *Proc. Acad. Sci. USSR: Chem. Sec. (Eng. Transl.)* **126**, 331 (1959).
[295] W. Steinkopf and P. J. Müller, *Ann. Chem. Liebigs* **448**, 210 (1926).
[296] H. D. Hartough, "Thiophene and Its Derivatives," p. 380. Interscience, New York, 1952.
[297] J. Tirouflet and J. P. Chané, *Compt. rend. acad. sci.* **245**, 80 (1957).

3. *Directing Effects of —I — M-Substituents in the 2-Position*

It can be seen from resonance structures (2) to (4) that a —I — M-substituent deactivates the 3- and 5-position most strongly in electrophilic substitution. If this deactivation of the 5-position is strong enough to overcome the activating effects of the sulfur in the 5-position, substitution will be directed to the 4-position to an increasing extent. Tirouflet and Fournari[298] studied the nitration of 2-substituted thiophenes of this type. The analysis was carried out polarographically, and the percentage of 4-isomer was as follows:

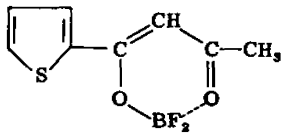
CHO	$COCH_3$	CN	COOH	$CH(OCOCH_3)_2$
75	52	43	31	14

These percentages follow the order of the σ-values of the substituents. On the other hand, Raynaud and Delaby obtained a mixture of 80% 4-nitro- and 20% 5-nitro-2-cyanothiophene, upon nitration of 2-cyanothiophene, which were separated by fractional crystallization.[246] In the nitration of 2-nitrothiophene, 85% 2,4-dinitrothiophene and 15% 2,5-dinitrothiophene is obtained.[197,298] The erroneous statement, in Hartough's monograph, that 2,5-dinitrothiophene is the main product, should be noted.[299] Nitration of 2-thiophenesulfonyl chloride gives about 75% of the 4-isomer and 25% of the 5-isomer,[196] whereas in the sulfonation of 2-nitrothiophene apparently only the 4-isomer has been isolated.[196,289]

The most selective 4-substitution is obtained in the Friedel-Crafts isopropylation of 2-acetylthiophene, which under certain conditions gives as much as 99% of this isomer and 1% of the 5-isomer.[300] Another case of selective 4-substitution is the bromination of 2-thienyl alkyl ketones using the swamping catalyst effect[301] (i.e., brominating in the presence of excess $AlCl_3$ without solvent), which yields 43–63% of apparently isomer-free 4-bromo-2-thienyl alkyl ketones.[302,303] Goldfarb *et al.* also have applied this method to the chloromethylation of

[298] J. Tirouflet and P. Fournari, *Compt. rend. acad. sci.* **246**, 2003 (1958).
[299] H. D. Hartough, "Thiophenes and Its Derivatives," p. 221. Interscience, New York, 1952.
[300] E. C. Spaeth and C. B. Germain, *J. Am. Chem. Soc.* **77**, 4066 (1955).
[301] D. E. Pearson and H. W. Pope, *J. Org. Chem.* **21**, 381 (1956).
[302] Ya. L. Goldfarb and U. B. Volkenstein, *Doklady Akad. Nauk. S.S.S.R.* **128**, 536 (1959); *Chem. Abstr.* **54**, 7679 (1960).
[303] U. B. Volkenstein and Ya. L. Goldfarb, *Doklady Akad. Nauk S.S.S.R.* **138**, 115 (1961); *Chem. Abstr.* **55**, 21090 (1961).

2-acetylthiophene, which, however, yields a mixture consisting of 4-chloromethyl- and 5-chloromethyl-2-acetylthiophene in the proportion of 4.3:1.[304,305] The structures of the compounds obtained in these experiments, as in Goldfarb's other work, have been proved by transformation to thiophenes of known structures or by Raney nickel desulfurization. Chloromethylation of 2-acetylthiophene, as well as methyl 2-thiophenecarboxylate, in the usual way with formalin and hydrochloric acid, proceeds very sluggishly and occurs predominantly in the 5-position as proved by the isolation of 2,5-thiophenedicarboxylic acid upon oxidation with permanganate.[306] Vinylthiophene, however, was chloromethylated in the side chain.[306] The acetylation of 2-acetylthiophene with acetic anhydride and BF_3 does not give 2-triacetylthiophene[307] but 3-oxo-1,2′-thienyl-but-1-enyloxyboron difluoride (**105**).[308] The structure was proved by preparing (**105**) from 2-thenoyl acetone and BF_3.[308]



[*105*]

The amount of 4-substitution is in certain cases even more strongly dependent upon the type of reaction. Thus the bromination of 2-thiophenealdehyde gives only 5-bromo-2-thiophenealdehyde.[309,310] The reason for this has been discussed.[21] Also 2-thiophenecarboxylic acid gives the 5-isomer upon bromination and chlorination.[311]

Whereas a +M-substituent, as mentioned before, strongly activates

[304] Ya. L. Goldfarb and U. B. Volkenstein, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* p. 2238 (1960); *Chem. Abstr.* **55**, 14223 (1961).
[305] Ya. L. Goldfarb and U. B. Volkenstein, *Zhur. Obshchei Khim.* **31**, 616 (1961); *Chem. Abstr.* **55**, 24712 (1961).
[306] R. Lukes, M. Janda, and K. Kefurt. *Collection Czechoslov. Chem. Communs.* **25**, 1058 (1960).
[307] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.* **70**, 867 (1948).
[308] G. M. Badger and J. M. Sasse, *J. Chem. Soc.* p. 746 (1961).
[309] S. Gronowitz, *Arkiv Kemi* **8**, 87 (1955).
[310] J. Lamy, D. Lavit, and N. P. Buu-Hoi, *J. Chem. Soc.* p. 4202 (1958).
[311] J. F. Bunnett, D. M. Bachman, L. P. Snipper, and J. H. Maloney, *J. Am. Chem. Soc.* **71**, 1493 (1949).

the 3-position, a —M-substituent strongly deactivates that position. Thus 2-thiophenecarboxylic acid can only be brominated to 4,5-dibromo-2-thiophenecarboxylic acid. Attempts to introduce a bromine in the 3-position led to the elimination of the carboxyl group.[312] Nitration of 4,5-dibromo-2-thiophenecarboxylic acid yields 4,5-dibromo-2-nitrothiophene.[247] In the benzene series, on the other hand, the main by-product in electrophilic substitution of —I—M-substituted compounds is the *ortho* isomer.[313]

4. *Directing Effects of ±I + M-Substituents in the 3-Position*

The halogens direct exclusively to the 2-position. 3-Bromothiophene is nitrated,[314] acylated,[247] and brominated[232] in the 2-position. However, in 3-alkylsubstituted thiophenes the difference in reactivity of the 2- and 5-positions is small. 3-Methylthiophene gives upon acylation[315] and formylation[44] a mixture consisting of about 80% 3,2-isomer and 20% 3,5-isomer. Acylation of 3-isopropylthiophene gives 31% 3-isopropyl-2-acetylthiophene and 48% 3-isopropyl-5-acetylthiophene.[300] Formylation and acetylation of 3-*t*-butylthiophene is claimed to give a single aldehyde and ketone, respectively, which without proof were taken to be 4-*t*-butyl-2-thiophenealdehyde and 4-*t*-butyl-2-acetylthiophene.[316] The fact that the ketone underwent a Pfitzinger reaction with isatin strengthens this assignment.[316] Nitration of 3-thenyl acetate gives a mixture of the 2- and 5-isomers, of which only the former was obtained pure in 30% yield.[317] The nitration of β-3-thienylacrylic acid also leads to a mixture of isomers.[317] In the bromination of 3-methylthiophene, on the other hand, only the 2-isomer is obtained.[318]

The substitution reactions of 3-acetamidothiophene have been extensively investigated.[319] From the bromination with *N*-bromosuccinimide and from the chlorination with sulfuryl chloride or *N*-chlorosuccinimide only the 2-isomers were obtained, the structure of which

[312] R. Bonz, *Ber. deut. chem. Ges.* **18**, 2308 (1885).
[313] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 262. Bell and Sons, London, 1949.
[314] C. D. Hurd and H. J. Anderson, *J. Am. Chem. Soc.* **75**, 3517 (1953).
[315] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.* **69**, 3093 (1947).
[316] M. Sy, N. P. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.* p. 21 (1955).
[317] W. Raich and C. Hamilton, *J. Am. Chem. Soc.* **79**, 3800 (1957).
[318] W. Steinkopf and H. Jacob, *Ann. Chem. Liebigs* **516**, 273 (1934).
[319] E. Campaigne and P. A. Monroe, *J. Am. Chem. Soc.* **76**, 2447 (1954).

were confirmed by their unequivocal synthesis via Hofmann rearrangements of the corresponding 2-bromo- and 2-chloro-3-thenamides.[319] Bromination with bromine in acetic acid led directly to disubstitution yielding 2,5-dibromo-3-acetylaminothiophene.[319] Iodination with iodine monochloride and nitration with nitric acid gave monosubstitution products to which, by analogy, the structures of 3-acetamido-2-iodo- and 3-acetamido-2-nitrothiophene were assigned.[319] As with 2-acetamidothiophene, the 3-isomer underwent diazo coupling with *p*-nitrophenyldiazonium chloride.[319] From the Friedel-Crafts succinoylation of 3-acetamidothiophene, two isomers have been isolated in 17 and 5% yield, the structures of which apparently have not been proved.[320]

5. *Directing Effects of —I—M-Substituents in the 3-Position*

From resonance structure (12) it is obvious that a —I—M-substituent strongly deactivates the 2-position toward electrophilic substitution, and one would thus expect that monosubstitution occurs exclusively in the 5-position. This has also been found to be the case in the chlorination, bromination, and nitration of 3-thiophenecarboxylic acid.[321] Upon chlorination and bromination a second halogen could be introduced in the 2-position, although further nitration of 5-nitro-3-thiophenecarboxylic acid could not be achieved.[321] Similarly, 3-thiophene aldehyde has been nitrated to 5-nitro-3-thiophene aldehyde,[44] and it is further claimed that 5-bromo-3-thiopheneboronic acid is obtained upon bromination of 3-thiopheneboronic acid.[239]

The ease with which electrophilic substitution occurs in position 4 in thiophenes containing a —I—M-substituent in position 3, if the reactive α-positions are blocked with halogens or methyl groups, in contrast to the difficulty of achieving such substitution in the 3-position of a —I—M 2-substituted thiophene was noticed already by Steinkopf *et al.*[322] They easily dinitrated and disulfonated 2,5-dimethylthiophene and 2,5-dibromothiophene.[323,324] These facts were explained by the present author after considering the resonance forms

[320] R. Motoyama, K. Sato, J. Ose, H. Wada, S. Nishimura, and E. Imoto, *Nippon Kagaku Zasshi* **78**, 794 (1957); *Chem. Abstr.* **54**, 22560 (1960).
[321] E. Campaigne and R. C. Bourgeois, *J. Am. Chem. Soc.* **76**, 2445 (1954).
[322] W. Steinkopf, "Die Chemie des Thiophens," p. 26. Theodor Steinkopff, Dresden and Leipzig, Germany, 1941.
[323] W. Steinkopf, H. Jacob, and H. Penz, *Ann. Chem. Liebigs* **512**, 136 (1934).
[324] W. Steinkopf, I. Poulsson, and O. Herdey. *Ann. Chem. Liebigs* **536**, 128 (1938).

(11) to (14) as contributing to the structure of a —I—M 3-substituted thiophene.[21] From the low weight of resonance form (14) it is evident that such a substituent does not strongly deactivate position 4. Molecular orbital calculations by Melander[20] on the π-electron distribution and localization energies for 3-nitrothiophene led to the same conclusions.

Additional examples of the reactivity of the 4-position in thiophenes with —I+M-substituent in the 3-position are provided by the bromination of 3-thiophenecarboxylic acid to 2,4,5-tribromothiophenecarboxylic acid[66] and the recent diacetylation of 2,5-dimethylthiophene by Goldfarb *et al.*,[325] who used the swamping catalyst effect of $AlCl_3$. The acylation can also be carried out stepwise and an 87% yield of 2,5-dimethyl-3,4-diacetylthiophene was obtained from 2,5-dimethyl-3-acetylthiophene.[325] Compounds with different acyl groups have been prepared in this manner.[325]

C. Electrophilic Substitution of Compounds Containing Several Thiophene Rings

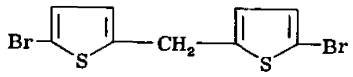
The acetylation and formylation of 2,2′-bithienyl give monosubstitution in the 5-position.[326,326a] Disubstitution is easily achieved and, in some cases, difficult to avoid as the deactivating effect of a substituent is not very strongly transmitted to the other ring.[326] The nitration of 2,2′-bithienyl has recently been studied.[327]

Acetylation of 2,3′-bithienyl occurs in the 5-position, which is in accordance with considerations on the localization energies.[328] The structure was proved by hypochlorite oxidation followed by Raney nickel desulfurization of the 5-carboxy-2,3′-bithienyl.[328]

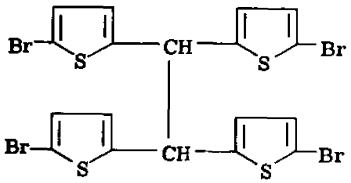
Bromination of di-2-thienylmethane is best achieved with a bromide–bromate mixture in a heterogenous system.[329] Conventional bromination with bromine in CCl_4 was accompanied by marked tar formation.[329] Bromination occurs in the 5- and 5′-positions of the rings as proved by the preparation of di-(5-bromo-2-thienyl)methane

[325] Ya. L. Goldfarb and V. P. Litvinov, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **30**, 2700 (1960).
[326] H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.* **78**, 1958 (1956).
[326a] E. Lescot, N. P. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.* p. 3234 (1959).
[327] C. Carpanelli and G. Leandri, *Ann. chim. (Rome)* **51**, 181 (1961).
[328] H. Wynberg and A. Bantjes, *J. Am. Chem. Soc.* **82**, 1447 (1960).
[329] Ya. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **26**, 3797 (1956).

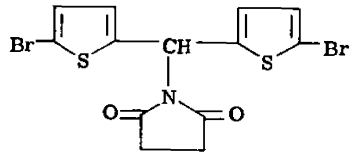
(106) from 2-bromothiophene, zinc chloride, and formalin in concentrated hydrochloric acid. *N*-Bromosuccinimide in the presence of benzoyl peroxide did not substitute in the methylene group. Even with (106) bromination in the methylene group could not be achieved. Instead, 1,1,2,2-tetra-(5-bromo-2-thienyl)ethane (107) and *N*-di-(5-bromo-2-thienyl)methylsuccinimide (108) were obtained. Diacetylation has also been achieved.[329a]



[106]



[107]

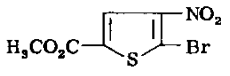


[108]

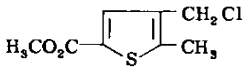
D. Electrophilic Substitution of Disubstituted Thiophenes

The position of substitution in disubstituted thiophenes can, in most cases, easily be deduced from the directing effect of each substituent. Thus with a +M-substituent in the 2-position and a —M-substituent in the 5-position, both substituents direct the entering group to the 3-position as is exemplified by the nitration of methyl 2-bromo-5-thiophenecarboxylate to methyl 2-bromo-3-nitro-5-thiophenecarboxylate (109)[247] or in the chloromethylation of methyl 2-methyl-5-thiophenecarboxylate to methyl 2-methyl-3-chloromethyl-5-thiophenecarboxylate (110).[330]

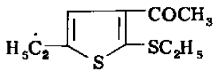
[329a] T. L. Cairns, B. C. McKusick, and V. Weinmayr, *J. Am. Chem. Soc.* **73**, 1270 (1951).
[330] M. Janda, *Collection Czechoslov. Chem. Communs.* **26**, 1889 (1961).



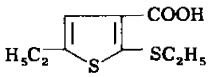
[109]



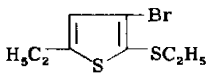
[110]



[111]



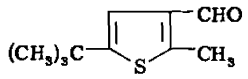
[112]



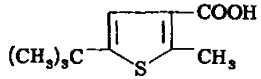
[113]

The stronger *ortho*-directing effect of the SC_2H_5 group compared with the C_2H_5 group is evident from the acetylation of 2-ethylthio-5-ethylthiophene to 2-ethylthio-3-acetyl-5-ethylthiophene (**111**) which was oxidized to the carboxylic acid (**112**) by alkaline hydrolysis of the pyridinium salt obtained upon reaction with pyridine and iodine.[285] The structure of the acid was proved by desulfurization to methylbutylacetic acid.[285] Bromination of 5-ethyl-2-ethylthiothiophene with bromide bromate solution gave 84% yield of 3-bromo-5-ethyl-2-ethylthiothiophene (**113**), the structure of which was proved by converting it to (**112**) through treatment with *n*-butyllithium and carbon dioxide.[285] Formylation also occurs *ortho* to the methylthio group.[331]

2-Methyl-5-*t*-butylthiophene is formylated in the 3-position to 2-methyl-5-*t*-butyl-3-thiophenealdehyde (**114**), as would be expected from the bulky nature of the *t*-butyl group.[332,333] The structure was



[114]

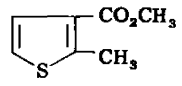


[115]

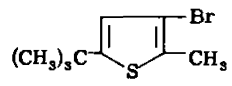
[331] Ya. L. Goldfarb, M. A. Kalik, M. L. Kirmalova, *Zhur. Obshchei Khim.* **30**, 1012 (1960); *Chem. Abstr.* **55**, 506 (1961).

[332] Ya. L. Goldfarb and I. S. Korsakova, *Bull. Akad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 481 (1954).

[333] Ya. L. Goldfarb and P. A. Konstantinov, *Bull. Akad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 113 (1957).



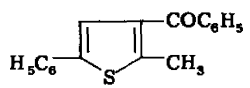
[116]



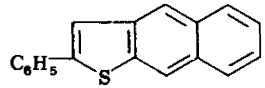
[117]

proved by preparing the acid (**115**) obtained by oxidizing (**114**) and also via Friedel-Crafts *t*-butylation of methyl 2-methyl-3-thiophenecarboxylate (**116**).[333] The same acid (**115**) was obtained from the Grignard reagent of the monobromo derivative of 2-methyl-5-*t*-butylthiophene (**117**), showing that bromination also occurs *ortho* to the methyl group.[333]

The $AlCl_3$-catalyzed benzoylation of 2-methyl-5-phenylthiophene to 2-methyl-3-benzoyl-5-phenylthiophene (**118**)[334] is of certain interest for comparison of the activating effect of an alkyl and phenyl group. The structure of (**118**) was proved in an original way by conversion to (**119**) by an Elbs reaction.[334]



[118]



[119]

Similar rules should apply for the substitution of 3,4-disubstituted thiophenes.

Further substitution of 2,4-disubstituted and most 2,3-disubstituted thiophenes occurs in the free α-position, except when a +M-substituent in the 3-position strengthens the 4-directing power of a —I—M-substituent in the 2-position. Thus methyl 3-methyl-2-thiophenecarboxylate is brominated in the 4-position[335] and 3-bromo-2-thiophenealdehyde is nitrated in the 4-position.[247] Recent investigations on the chloromethylation, sulfonation, mercuration, and nitration of 2,4-dichlorothiophene, which without proof are assumed to occur in the 5-position serves as examples of the reactivity of a 2,4-disubstituted thiophene.[178,336] Formylation with *N*,*N*-dimethylformamide and

[334] P. Demerseman, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.* p. 4193 (1954).

[335] W. Steinkopf and W. Nitschke, *Ann. Chem. Liebigs* **536**, 135 (1938).

[336] E. Profft and A. Kubat, *Ann. Chem. Liebigs* **634**, 185 (1960).

$POCl_3$ could not be achieved and in order to obtain chloromethylation the presence of anhydrous $ZnCl_2$ was necessary.[178,336]

Note added in proof: The compounds described as derivatives of 2,4-dichlorothiophene[178,336] are derivatives of 2,3-dichlorothiophene.[179a] Additional derivatives of 2,3-dichlorothiophene have been prepared.[336a-d]

E. Substitution with Elimination of Substituents

In the reactions of 2,5-disubstituted thiophenes elimination of an α-substituent occurs to a much greater extent than in the benzene series. The Friedel-Crafts acetylation of 5-bromo-2-ethylthiophene in the presence of $SnCl_4$ gives 2-ethyl-5-acetylthiophene.[333] Elimination of an α-bromine occurs also in the chloromethylation of 2,5-dibromothiophene, leading to a mixture of 2-bromo-5-chloromethylthiophene and 2,5-dibromo-3-chloromethylthiophene.[236] Bromine atoms at both the α-[272] and β-position[44] are exchanged for chlorine in the $POCl_3$-catalyzed formylation, so $POBr_3$ must be used instead.[247,272]

Another example is the replacement of halogen by the nitro group in the nitration of halogenated 2-acetamidothiophenes.[337]

Such eliminations do not occur with chloro compounds.[236,245] 2,5-Dichlorothiophene undergoes $AlCl_3$-catalyzed sulfonylation with benzenesulfonyl chloride.[338] Attempts to extend this reaction to thiophene, 2,5-dimethylthiophene, and 2-chloro-5-iodothiophene resulted in the formation of intractable tars even with other catalysts.[338] Sulfones of this type are often prepared in much better yields by using thiophenesulfonyl chlorides and benzenes in the Friedel-Crafts reaction.[338]

Carboxyl groups are easily removed during nitration especially at higher temperatures.[339,340] A detailed study on the nitration of 5-bromo-2-thiophenecarboxylic acid showed that the proportion of 2,4-dinitro-5-bromothiophene increased with the concentration of sulfuric and nitric acid.[340] The mechanism of this decarboxylative nitration

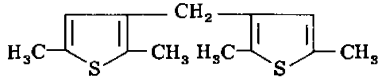
[336a] E. Profft and D. Gerber, *J. prakt. Chem.* No. 287, 8 (1962).
[336b] E. Profft and H. Mitternacht, *J. prakt. Chem.* No. 287, 13 (1962).
[336c] E. Profft and P. Lux, *J. prakt. Chem.* No. 287, 18 (1962).
[336d] E. Profft and H. E. Petzgold, *J. prakt. Chem.* No. 287, 26 (1962).
[337] H. M. Priestley and C. D. Hurd, *J. Am. Chem. Soc.* **69**, 1173 (1947).
[338] W. E. Truce and F. J. Lotspeich, *J. Am. Chem. Soc.* **77**, 3410 (1955).
[339] E. Campaigne and H. G. Grose, *J. Am. Chem. Soc.* **73**, 3812 (1951).
[340] R. Motoyama, K. Sato, and E. Imoto, *Nippon Kagaku Zasshi* **78**, 779 (1957); *Chem. Abstr.* **54**, 22559 (1960).

appears to be a direct electrophilic substitution by the nitronium cation.[339,340] The presence of substituents which lower the electron density at the 2-position or esterification prevent decarboxylative nitration.[340] The elimination of an α-carboxyl group on vigorous bromination of 4,5-dibromo-2-thiophenecarboxylic acid leading to tetrabromothiophene has already been mentioned.[312]

The elimination of alkyl groups during $AlCl_3$-catalyzed Friedel-Crafts reaction has also been noted. 2-Methyl-5-ethylthiophene has been obtained from the alkylation of 2,5-dimethylthiophene with ethyl bromide.[135] Acylation[332] and sulfonation[341] of 2-methyl-3,5-di-*t*-butylthiophene are unusual in that they occur with elimination of the *t*-butyl group in the β-position giving 2-methyl-3-acetyl-5-*t*-butylthiophene and 2-methyl-5-*t*-butyl-3-thiophenesulfonic acid. The structure of the sulfonation product was proved by its identity with that obtained upon sulfonation of 2-methyl-5-*t*-butylthiophene.[341] 2,5-Di-*t*-butylthiophene is monosulfonated normally in the 3-position. Under forcing conditions one *t*-butyl group is thrown out and 2-*t*-butyl-3,5-thiophenedisulfonic acid is obtained.[341] Through careful structure proof, Goldfarb *et al.* also showed that no rearrangements occurred during the formylation, acetylation, and bromination of 2,5-di-*t*-butylthiophene.[333]

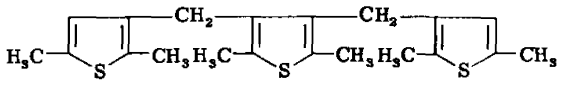
F. Miscellaneous Electrophilic Substitutions

The chloromethylation of 2,5-dimethyl- and 2,5-diethyl-thiophene both with chlorodimethyl ether and formaldehyde and hydrochloric acid gives a mixture of mono- and di-chloromethylated product.[342-344] The former reagent gives the larger proportion of monochloromethylated product.[343,344] If the chloromethylation is carried out in the presence of zinc chloride, **(120)** and **(121)** are obtained.[344]



[*120*]

[341] Ya. L. Goldfarb, L. V. Antik, and P. A. Konstantinov *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 627 (1956).
[342] R. Gaertner and R. G. Tonkyn, *J. Am. Chem. Soc.* **73**, 5872 (1951).
[343] P. Cagniant and D. Cagniant, *Bull. soc. chim. France* p. 713 (1953).
[344] Ya. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 487 (1956).

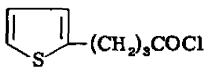


[121]

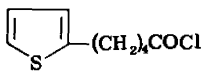
The sulfonating actions of pyridine-sulfur trioxide, pyridine-bis sulfur trioxide and dioxane sulfur trioxide on 2,5-dimethylthiophene have been compared.[345] Yields of 95% monosulfonic acid were obtained with the latter two reagents, whereas pyridine sulfur trioxide yielded only 75%.[345] 2-Methyl-3,5-diphenylthiophene resists formylation and $SnCl_4$-catalyzed acylation in contrast to 2,3,5-trimethylthiophene,[334] which is formylated and acylated quite easily.

G. Electrophilic Ring-Closure Reactions

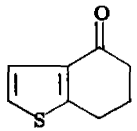
The acid chlorides of ω-(2-thienyl)substituted butyric (**122**) and valeric acids (**123**), as well as the corresponding 5-alkyl-2-thienyl-substituted compounds, undergo internal Friedel-Crafts reaction ($SnCl_4$,CS_2) at the 3-position in 70–80% yield, to give the corresponding cyclohexenones (**124**) and cycloheptenones (**125**).[212,346,347]



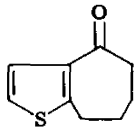
[122]



[123]



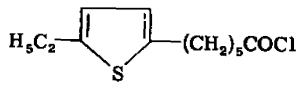
[124]



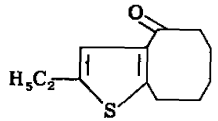
[125]

[345] A. P. Terent'ev and G. M. Kadatskii, *Zhur. Obshchei Khim.* **23**, 251 (1953); *Chem. Abstr.* **48**, 3339 (1954).
[346] P. Cagniant and D. Cagniant, *Bull. soc. chim. France* p. 62 (1953).
[347] P. Cagniant and D. Cagniant, *Bull. soc. chim. France* p. 680 (1955).

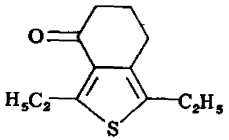
From ε-(5-ethyl-2-thienyl)caproic acid (**126**), however, only 8% of (**127**) is obtained. The acid chlorides of γ-(2,5-diethyl-3-thienyl)



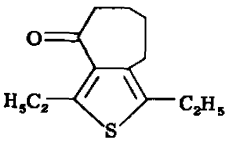
[126]



[127]

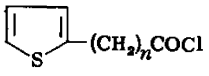


[128]

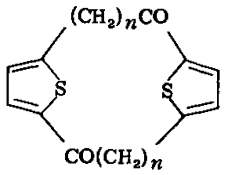


[129]

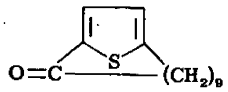
butyric acid and γ-(2,5-diethyl-3-thienyl)valeric acid react in the 4-position and give (**128**) and (**129**), respectively.[343]



[130]



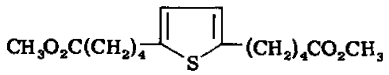
[131]



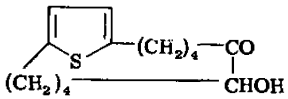
[132]

The Friedel-Crafts cyclization of ω-(2-thienyl)substituted longer fatty acids (**130**, $n = 5,8,9$) under high dilution conditions has been investigated by Goldfarb *et al.*[348,349] They used boiling ethereal $AlCl_3$, or $SnCl_4$ in benzene at +5°C for the cyclizations. In spite of high dilution, only products of intermolecular cyclization of two molecules of acid chloride (**131**) were obtained when $n = 5,8$, or 9.[348]

When $n = 9$, a yield as high as 17% (**131**, $n = 9$) was obtained.[349] Using $AlCl_3$ in CS_2, 10-(2-thienyl)decanoyl chloride (**130**, $n = 9$) gave, besides traces of (**131**, $n = 9$), 12.5% of (**132**).[349] Other ingenious methods for the preparation of compounds of type (**132**) have been worked out. Acyloin condensation of (**133**) with finely divided

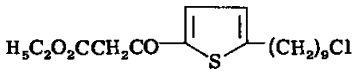


[*133*]

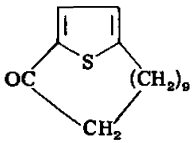


[*134*]

sodium in ether–xylene at 60°C gives 25–30% (**134**).[348] Finally, an



[*135*]



[*136*]

internal alkylation of the acetoacetate (**135**), followed by ketone splitting of the resulting macrocyclic β-ketoester yielded (**136**).[350]

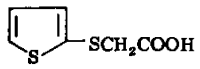
[348] Ya. L. Goldfarb, S. Z. Taits, and L. I. Bel'enkii, *Bull. Acad. Sci. S.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 1287 (1957).

[349] Ya. L. Goldfarb, S. Z. Taits, and L. I. Belenkii, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **29**, 3526 (1959).

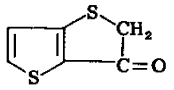
[350] S. Z. Taits and Ya. L. Goldfarb, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 1574 (1960).

Raney nickel desulfurization of the macrocyclic ketones or their reduction products confirmed the structures assigned to these compounds and simultaneously offers new methods for the synthesis of macrocyclic alicyclic compounds.[348-350]

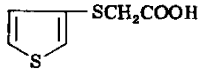
The cyclization of thienylthioacetic acids[351-353] and thienylthioacetaldehyde acetals[354-357] has been studied in connection with work on the chemistry of the thiophthenes. The cyclizations are achieved with P_2O_5,[354-357] concentrated H_2SO_4,[351,353] or anhydrous HF,[352] usually in low yields (10–15%). An interesting rearrangement has been discovered in the cyclization of 2-thienylthioacetic acid (**137**) with concentrated H_2SO_4 which leads to 2*H*-thieno[3,2-*b*]thiophene-3-one (**138**), identical with the product obtained upon cyclization of 3-thienylthioacetic acid (**139**).[353] The structure of (**138**) has been



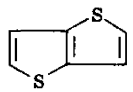
[*137*]



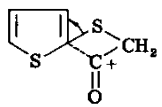
[*138*]



[*139*]



[*140*]



[*141*]

proved by conversion to the known thiophthene (**140**). It has been suggested that this rearrangement involves electrophilic substitution by the cationoid carbonyl carbon at the ring α-carbon carrying the sulfur atom, with simultaneous rearrangement of the sulfur to the 3-position (**141**).[353] This type of rearrangement was found first in the

[351] F. Challenger and J. L. Holmes, *J. Chem. Soc.* p. 1837 (1953).

[352] O. Dann and W. Dimmling, *Chem. Ber.* **87**, 373 (1954).

[353] S. Gronowitz and P. Moses, *Acta Chem. Scand* **16**, 155 (1962).

[354] V. V. Ghaisas and B. D. Tilak, *Proc. Indian Acad. Sci.* **39A**, 14 (1954).

[355] V. V. Ghaisas and B. D. Tilak, *Current Sci.* (*India*) **22**, 184 (1953).

[356] L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Research* (*India*) **18B**, 371 (1959).

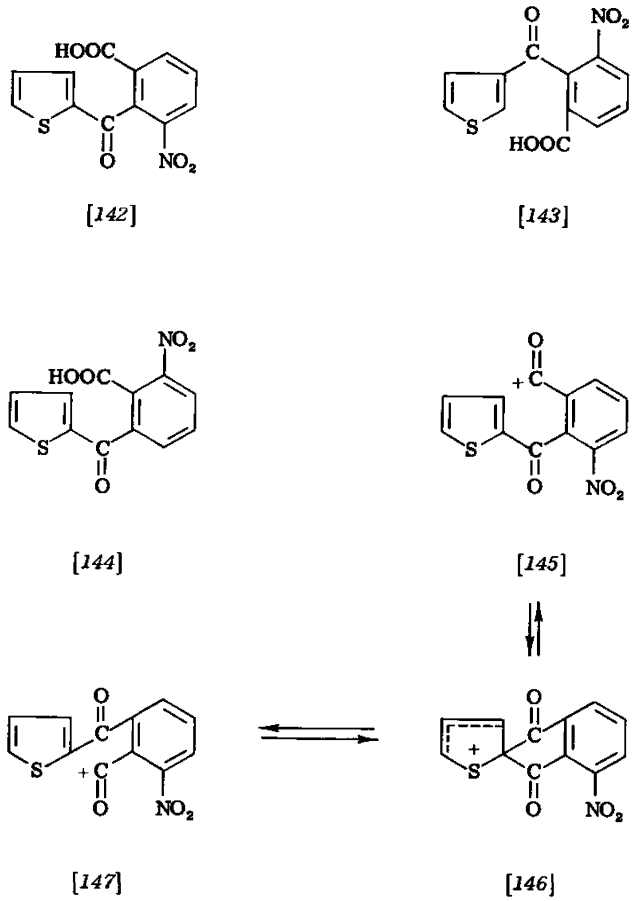
[357] L. J. Pandya and B. D. Tilak, *Chem. & Ind.* (*London*) p. 981 (1958).

pyrrole series[358,359] and is probably connected with the considerably greater reactivity of the α-position over the β-position in electrophilic substitution.

The much greater reactivity of the α-position is also responsible for a rearrangement which occurs in the reaction of 3-thienylzinc or 3-thienylcadmium with acetic chloride.[237] Besides substitution at the metal-organic bond, electrophilic aromatic substitution occurs in the 2-position, the metalorganic compound acting as an internal Lewis acid. Thus, from 3-thienylzinc and acetyl chloride, a mixture of 65% 2-acetylthiophene and 31% 3-acetylthiophene was obtained.[237] The greater difference in reactivity of the α- and β-positions in furan as compared to thiophene is obvious from the fact that only 2-acetylfuran has been found in the reaction of 3-chloromercuryfuran and acetyl chloride.[360] This rearrangement has also been found in the benzene series with the cadmium reagent from *m*-bromoanisole,[361] and the mechanism has recently been demonstrated by Dauben and Collette.[362]

Complex rearrangements occur in the treatment of substituted *o*-(2-thenoyl)benzoic acids with concentrated sulfuric acid (Hayashi rearrangement). Careful investigations by Newman and Ihrman[363] have shown that the claim by Schroeder and Weinmayer[364] that 3-nitro-2-(2-thenoyl)benzoic acid (**142**) is rearranged to 3-nitro-2-(3-thenoyl)benzoic acid (**143**) before ring closure to a thiophanthraquinone is erroneous. Newman and Ihrman also demonstrated that (**142**) is rearranged to 6-nitro-2-(thenoyl)benzoic acid (**144**) contrary to the reports of Brown *et al.*[365] claiming that (**144**) is rearranged to (**142**). The mechanism of the Hayashi rearrangement is schematically indicated in (**145**) to (**147**). The key-intermediate is (**146**), and, again, one could say that the high reactivity of the α-position over the β-position is the driving force behind the rearrangement.[363] Rearrangement is, of course, possible if any group *ortho* or *meta* to the carbonyl group is present in the benzene ring. Also, instead of the thiophene ring, another unsymmetrical substituent, such as a substituted benzene ring, may be involved in other cases. These structural features are of importance in determining the position of the equilibrium **145** $\rightleftharpoons$ **146** $\rightleftharpoons$ **147** in the general case, and therefore, for the structure of the thiophanthraquinone formed.[363] (2-Thenoyl)benzoic acids, the intermediates in the preparation of the thiophanthraquinones, which are of interest as dyes, have been pre-

[358] S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *J. Org. Chem.* **26**, 2615 (1961).
[359] S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi* **18**, 151 (1961).
[360] S. Gronowitz and G. Sörlin, *Arkiv Kemi* **18**, 515 (1962).
[361] L. H. Klemm, R. Mann, and C. D. Lind, *J. Org. Chem.* **23**, 349 (1958).
[362] W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.* **81**, 967 (1959).
[363] M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.* **80**, 3652 (1958).
[364] H. E. Schroeder and V. Weinmayr, *J. Am. Chem. Soc.* **74**, 4357 (1952).
[365] R. Goncalves, M. R. Kegelman, and E. V. Brown, *J. Org. Chem.* **17**, 705 (1952).

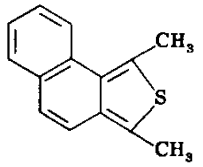


pared by the reaction of substituted phthalic anhydrides with thiophenemagnesium compounds,[366] or through the Friedel-Crafts reaction between thiophenes and phthalic anhydrides[367] or suitable acid chlorides,[368] such as 1-bromo-2-naphthoyl chloride. The bromine was then, via the nitrile, converted to a carboxyl group.[368]

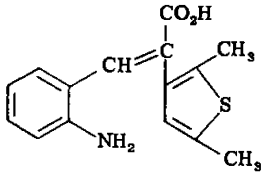
V. Other Substitution Reactions

A. Radicaloid Substitution

Radicaloid substitution has not been extensively studied in the thiophene series. Molecular orbital calculations indicate that substitution should occur in the α-position.[20] This has been found to be the case in the Gomberg-Bachmann coupling of diazohydroxides with thiophenes which has been used for the preparation of 2-(*o*-nitrophenyl)thiophene,[369] 2-(*p*-toluyl)thiophene,[370,371] and 2-(*p*-chlorophenyl)thiophene.[371] Coupling in the β-position has been used for the preparation of 1,3-dimethyl-4,5-benzisothionaphthene (**148**) from 2-amino-α-(2,5-dimethyl-3-thienyl)cinnamic acid (**149**).[372] A recent investigation describes the homolytic phenylation of 2- and 3-phenyl-



[*148*]



[*149*]

thiophene.[373] Benzyl radicals derived from di-(9-benzyl-9-fluorenyl) peroxide react with thiophene to give 2-benzylthiophene containing,

[366] R. Goncalves and E. V. Brown, *J. Org. Chem.* **17**, 698 (1952).
[367] A. T. Peters and D. Walker, *J. Chem. Soc.* p. 1525 (1957).
[368] M. C. Kloetzel, W. King, W. J. Wasserman, C. K. Warren, and P. A. Larssen, *J. Org. Chem.* **26**, 607 (1961).
[369] P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.* **73**, 2626 (1951).
[370] N. P. Buu-Hoi and D. Lavit, *Bull. soc. chim. France* p. 290 (1958).
[371] N. P. Buu-Hoi and N. Hoan, *Rec. trav. chim.* **69**, 1455 (1950).
[372] O. Dann and H. Distler, *Chem. Ber.* **87**, 365 (1954).
[373] J. Degani, M. Polloti, and A. Tundo, *Ann. chim. (Rome)* **51**, 434 (1961).

significantly, less than 5% of the 3-isomer.[374] The compounds formed by the decomposition of 2-thenoyl peroxide in aromatic solvents can be largely attributed to the reaction of 2-thenoxyloxy radicals.[375] In thiophene, 2-thienyl thenoate and 2,2′-bithienyl were obtained, the latter providing evidence for the generation of 2-thienyl radicals.[375]

The gas-phase bromination of thiophene at 750°C gives, somewhat unexpectedly, 3-bromothiophene in low yield.[314] 2-Methylthiophene was brominated exclusively in the methyl group at 400 or 600°C. It is possible that several of the nuclear brominations with *N*-bromosuccinimide, mentioned earlier, are radicaloid in nature.

B. Nucleophilic Substitutions

1. *Aromatic Nucleophilic Substitutions*

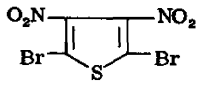
The halogens of halothiophenes are more labile than those of the corresponding benzenes in accordance with theoretical considerations[20] which indicate that thiophenes should also undergo nucleophilic substitutions more rapidly than benzenes. Hurd and Kreuz[376] found that in qualitative experiments 3,5-dinitro-2-chlorothiophene was more reactive toward piperidine and methanolic potassium hydroxide than 2,4-dinitrochlorobenzene. A quantitative study on the reaction of the six isomeric bromonitrothiophenes with piperidine[70] (Table V) shows that the thiophenes react about one thousand times

TABLE V
Rate Constants and Relative Rates of Bromonitrophenes and Bromonitrobenzenes with Piperidine at 25°C

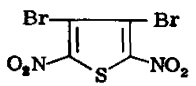
Compounds	Rate constants of pseudo first order	Relative rate
4-Bromo-2-nitrothiophene	2.44×10^{-3}	1360
5-Bromo-2-nitrothiophene	5.10×10^{-2}	284×10^{2}
2-Bromo-3-nitrothiophene	1×13	632×10^{3}
3-Bromo-2-nitrothiophene	4×48	250×10^{4}
5-Bromo-3-nitrothiophene	Very fast	—
4-Bromo-3-nitrothiophene	Very fast	—
m-Bromonitrobenzene	1.79×10^{-6}	1
p-Bromonitrobenzene	3.31×10^{-4}	185
o-Bromonitrobenzene	2.91×10^{-3}	1620

[374] J. I. G. Cadogan, D. H. Hey, and W. A. Sanderson, *J. Chem. Soc.* p. 3203 (1960).
[375] M. C. Ford and D. Mackay, *J. Chem. Soc.* p. 4620 (1957).
[376] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.* **74**, 2965 (1952).

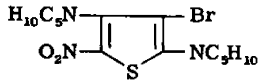
faster than the corresponding benzenes, when the formation of bromide ion was measured. The very high reactivity of 4-bromo-3-nitrothiophene and especially of 5-bromo-3-nitrothiophene is rather surprising.[70] The similar reactivity of α- and β-bromines (in fact 2-nitro-3-bromothiophene reacts faster than 3-nitro-2-bromothiophene) is not expected from theoretical considerations.[20] On the other hand, recent investigations by Leandri *et al.*[377] indicate a large difference in the reactivity of the α- and β-positions. Thus, although the halogens of 2,5-dibromo-3,4-dinitrothiophene (**150**) react smoothly with various nucleophiles, such as piperidine, arylthiolate, or arylsulfinate, yielding mono- or disubstituted 3,4-dinitrothiophenes, depending on reagents and conditions, 2,5-dinitro-3,4-dibromothiophene (**151**) reacts with nucleophiles with elimination of an α-nitro group.[377] The



[*150*]



[*151*]

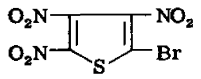


[*152*]

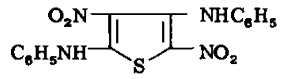
importance of determining the thiophene products obtained to understand the nucleophilic reactivity of thiophenes is further evident from the fact that on continued substitution of (**151**), a β-halogen reacts.[377] Thus, refluxing (**151**) with excess piperidine for 12 hr is claimed to give 2,4-dipiperidino-3-bromo-5-nitrothiophene (**152**).[377] High reactivity of nitro groups has also been found in 2-bromo-3,4,5-trinitrothiophene (**153**) which with aniline yields 2,4-dinitro-3,5-dianilinothiophene (**154**).[378] The reactivity of (**153**) toward even weak nucleophiles is so great that it can be crystallized only from concentrated nitric acid.[378]

[377] G. Leandri, D. Spinelli, and C. dell'Erba, *Ann. chim.* (*Rome*) **50**, 1597 (1960); *Chem. Abstr.* **55**, 21091 (1961).
[378] A. H. Blatt, N. Gross, and E. W. Tristram, *J. Org. Chem.* **22**, 1588 (1957).

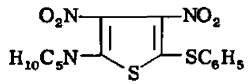
Nucleophilic substitution has been used for the preparation of many thiophenes. For instance, 2-phenylthio-3,4-dinitro-5-piperidinothiophene (**155**) has been prepared[377] through stepwise reaction of (**150**) with different nucleophiles. Nitrothienols and derivatives of them have been obtained from halogenated nitrothiophenes.[376] Allyl ethers have been prepared by the reaction of 5-chloro-4-nitro-2-acetylthiophene, 3-nitro-2-chlorothiophene, and 2-nitro-3-bromothio-



[*153*]



[*154*]



[*155*]

phene with sodium allyloxide.[379] *N*-3,5-Dinitro-2-thienylglycine has been obtained from 2-bromo-3,5-dinitrothiophene and glycine ester hydrochloride in ethanol in the presence of ZnO.[380] 2-Chlorothiophene and 2-bromo-5-nitrothiophene did not react.[380]

Halothiophenes, which are not activated through the presence of —I—M-substituents, undergo substitution smoothly under more forcing conditions with copper salts in pyridine or quinoline. Hence 3-cyanothiophene[233] and 5-methyl-2-cyanothiophene[381] have been obtained from the corresponding bromo compounds. 2-Bromothiophene reacts readily with aliphatic cuprous mercaptides in quinoline at 200°C to give thioethers in high yields.[382] The use of the copper-catalyzed Williamson synthesis of alkoxythiophenes from iodo- or bromo-thiophenes and alcoholate has been mentioned before.[62,274,276] The reaction of 2-bromothiophene with acetanilide in nitrobenzene in

[379] C. D. Hurd and H. J. Anderson, *J. Am. Chem. Soc.* **76**, 1267 (1954).
[380] J. M. Tien and I. M. Hunsberger, *J. Org. Chem.* **25**, 2056 (1960).
[381] A. Vecchi and G. Melone, *J. Org. Chem.* **22**, 1636 (1957).
[382] R. Adams and A. Ferretti, *J. Am. Chem. Soc.* **81**, 4927 (1959).

the presence of copper and anhydrous potassium carbonate gave *N*-acetyl-*N*-phenyl-2-thienylamine in 14% yield.[383] 2-Bromothiophene reacts vigorously with sodium acetylide in liquid ammonia.[384] However, the main product was not the expected 2-thienylacetylene but tetrabromothiophene. 3-Bromothiophene did not react.[384]

The great lability of the halogens makes them the most suitable blocking agent in the thiophene series as they can be removed with many reagents. The reductive dehalogenation of substituted bromothiophenes with zinc amalgam, sodium amalgam, and aluminium amalgam has been compared and the influence of the substituents discussed.[385] The rates of debromination were determined by polarographic half-wave potentials.[385] Hypophosphorous acid and copper in acidic media have been used for the removal of halogens[378] and, with copper in quinoline, debromination and decarboxylation have been achieved simultaneously.[247] Halogens are also removed during reduction of halogenated thenoic acids with $LiAlH_4$.[321]

Large differences between the reactivities of α- and β-positioned halogens have been found which can be utilized for preparative purposes. Through the selective removal of α-halogens with zinc powder in acetic acid, 3,4-dibromothiophene, 3-methyl-4-bromothiophene, and 2-methyl-3-bromothiophene are conveniently prepared from tetrabromothiophene, 3-methyl-2,4,5-tribromothiophene, and 2-methyl-3,5-dibromothiophene, respectively.[44,240] It was also noted that, whereas a β-positioned bromine facilitated the removal of other bromines (α as well as β), the converse was the case with a methyl group in the β-position, in accordance with the nucleophilic nature of these reductions.[240] In the reduction of the nitro groups of the three isomeric bromo-3-nitrothiophenes with tin and hydrochloric acid, reductive dehydrobromination occurred simultaneously with the *o*-bromo isomers but not with 5-bromo-3-nitrothiophene.[386] Exchange of bromine for chlorine was also observed in some cases during such reductions.[386]

Whereas halogens in the α-positions are removed in the Wolff-Kishner reduction,[387] this is not the case with β-positioned bromine.[133]

[383] R. R. Estes and P. Panzera, *J. Am. Chem. Soc.* **74**, 853 (1952).
[384] A. Vaitiekunas and F. F. Nord, *J. Am. Chem. Soc.* **75**, 1764 (1953).
[385] R. Motoyama, J. Ose, H. Wada, and E. Imoto, *Nippon Kagaku Zasshi* **78**, 784 (1957); *Chem. Abstr.* **54**, 22560 (1960).
[386] R. Motoyama, S. Nishimura, and E. Imoto, *Nippon Kagaku Zasshi* **78**, 788 (1957); *Chem. Abstr.* **54**, 22560 (1960).
[387] N. P. Buu-Hoi, N. D. Xuong, and N. Hoan, *Rec. trav. chim.* **71**, 285 (1952).

2. *Metalation of Thiophenes with Organolithium Compounds (Nucleophilic Substitution on Hydrogen)*

The metalation of thiophene with *n*-butyllithium, discovered by Gilman *et al.*,[185] gives rapidly 2-thienyllithium in almost quantitative yield. The following mechanism has been suggested.[235] After coordination of the metalating agent to the ring sulfur, the most acidic (most positively polarized) hydrogen is attacked by the carbanion of the metalating agent. This mechanism is in accordance with the exclusive α-metalation of thiophenes, with the directive influence of substituents in the 3-position[21] and with results of a study of the hydrogen isotope effect in the metalation of thiophene.[388] Metalation of tritium-marked thiophene gave an isotopic rate ratio $k_T/k_H \leqslant 0.17$ in accordance with nucleophilic activity of the metalating agent, thus showing that the elimination of hydrogen is the rate-determining step.[388]

The α-selectivity is illustrated by the fact that 2-alkyl-,[38,44,285,389] 2-methoxy-,[44,274] and 2-alkylthio-thiophenes[389] and alkyl thenyl sulfides[282,390] are metalated exclusively in the 5-position. In electrophilic aromatic substitution, as previously mentioned, an appreciable amount of 3-substitution is obtained with some of these groups. After acetalization ketones can also be metalated.[304] Thus from the diethyl ketal of 2-acetylthiophene, 2-acetyl-5-thiophenealdehyde was obtained after metalation with *n*-butyllithium followed by the reaction of the metalorganic compound with *N*,*N*-dimethylformamide.[304]

Competitive metalation of thiophene and 2-methylthiothiophene with a deficiency of *n*-butyllithium gave only 2-methylthio-5-thiophenecarboxylic acid, showing the activating effect of the methylthio group.[389]

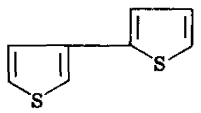
When both α-positions are blocked, the highly specific reactivity toward organolithium compounds disappears and metalation depends on the kind of α-substituents present. Thus whereas 2,5-dimethylthiophene is not metalated at all, 2-methoxy-5-methylthiophene is metalated in the 3-position,[274] similar to the known *ortho* metalation of anisole. On the other hand, 5-methyl-2-methylthiothiophene is also metalated (in low yield) in the 3-position,[389] in contrast to thioanisole

[388] S. Gronowitz and K. Halvarson, *Arkiv Kemi* **8**, 343 (1955).
[389] Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **29**, 3592 (1959).
[390] Ya. L. Goldfarb, G. I. Gorushkina, and B. P. Fedorov, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 1925 (1959).

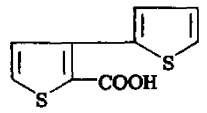
which is metalated in the side chain. Similarly, whereas di-2-thienylmethane can be mono- or di-metalated in the free α-positions[391] and 5-methyl-2,2′-dithienylmethane in the remaining free α-position, in high yield,[391] 5,5′-dimethyl-2,2′-dithienylmethane is metalated in low yield in the 3-position.[392] Diphenylmethane, on the other hand, is metalated in the methylene group, which indicates that the β-hydrogens of thiophenes are also more acidic than those of benzene. 2,2′-Bithienyl can be mono- or di-metalated with phenyllithium.[328]

The directing effect of substituents in the 3-position has been studied in order to determine the mechanism of metalation with organolithium compounds and to evaluate the preparative value of this reaction in the thiophene series.[21] The metalated compounds were isolated in the customary manner as the carboxylic acids produced by the reaction with carbon dioxide. 3-Methylthiophene is metalated predominantly in the 5-position,[44,235,393] and competitive experiments with thiophene indicated that it is metalated more slowly than thiophene.[235] This is expected as the +I effect of the methyl group increases preferentially the electron density at the 2-position making the hydrogen in this position less acidic than in the 5-position and making both the 2- and 5-hydrogen less acidic than in thiophene.[235] 3-Methoxythiophene,[63] 3-methylthiothiophene,[43] and 3-bromothiophene[235] are metalated in the 2-position. This has been ascribed to the —I effect of these substituents, which during the reaction is also strengthened by the inductomeric effect in the same direction.[21] The great importance of the inductive effect in the metalation reaction has been pointed out by Wittig.[394] Metalation also occurs in the sterically hindered 2-position of 3-*t*-butoxythiophene.[244] However, 3-phenylthiophene gives, upon metalation and carbonation, a mixture of 5- and 2-acid, the former dominating, which is somewhat unexpected as the phenyl group generally is considered as a —I-substituent.[21] It is possible that steric effects are responsible for this. Wynberg and Bantjes[328] studied the metalation of 2,3′-bithienyl (**156**) and found that metalation occurred in the 2′- and 5′-positions, giving 52% yield

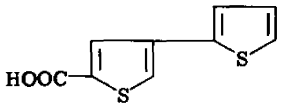
[391] Ya. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **25**, 1321 (1955).
[392] Ya. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **29**, 881 (1959).
[393] J. Sicé, *J. Org. Chem.* **19**, 70 (1954).
[394] G. Wittig, *Angew. Chem.* **66**, 10 (1954).



[*156*]



[*157*]



[*158*]

of 2′-carboxy-2,3′-bithienyl (**157**) and 39% of 5′-carboxy-2,3′-bithienyl (**158**), while electrophilic substitution occurred in the 5-position.[328] The high yield of (**157**) has been ascribed to electron attraction by thiophene as an *ortho*-substituent. These authors also point out that coordination of the lithium with the sulfur of either ring prior to exchange at the 2′-position may influence the extent of exchange in this position.[328] 3,3′-Bithienyl gives a complex mixture of mono- and di-carboxylic acids upon metalation.[133] Metalation of methyl 3-thienyl sulfone occurred in the side chain, showing that the activating effect on metalation of the sulfone group is stronger than that of the ring sulfur.[43]

Thiophene is also metalated by a benzene-soluble ethyl sodium–diethyl zinc complex. Upon carbonation, 55% of 2-thiophenecarboxylic acid was obtained.[395]

3. *Halogen–Metal Interconversion between Halothiophenes and Metalorganic Compounds (Nucleophilic Substitution on Halogen)*

Halogen–metal interconversion between bromothiophenes and *n*-butyllithium, leading to thienyllithium derivatives and *n*-butyl bromide, occurs almost instantaneously and in very high yield even at

[395] J. H. Ludwig and H. Schulze, *J. Org. Chem.* **24**, 1573 (1959).

—70°C.[235,396-398] This is of great preparative importance as the Grignard reagent of 3-bromosubstituted thiophenes and the dibromothiophenes can be obtained only by the entrainment method and with inferior yields.[61,396,397,399] The mechanism of the entrainment reaction has been shown to differ from halogen–metal interconversion.[400]

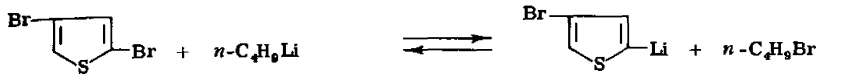
The interconversion with di- and tri-bromothiophenes is very selective. Thus 2,3,5-tribromothiophene gives exclusively 3,5-dibromo-2-thienyllithium,[396] the hydrolysis of which affords a very convenient synthesis of 2,4-dibromothiophene. Similarly, 2,4-[396,398] and 2,3-dibromothiophene[398] give interconversion selectively with the α-bromine.

With excess *n*-butyllithium, 2,5-[357,401] and 3,4-dilithiothiophene[398] have been obtained from 2,5- and 3,4-diiodothiophene, respectively.

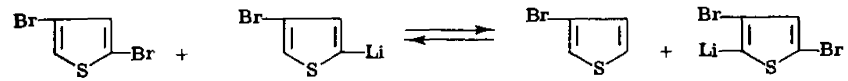
The stability of the lithium reagents derived from 3-bromothiophene and 3,4- and 2,4-dibromothiophene through interconversion with *n*-butyllithium has been studied.[398] In these compounds the lithium does not replace the most acidic hydrogen and rearrangements can, therefore, be expected. It was found, however, that at —70°C, 3-thienyllithium, 4-bromo-2-thienyllithium, 3-bromo-2-thienyllithium, and 3-bromo-4-thienyllithium were stable for at least 10 hr when properly prepared by addition of the bromothiophenes to the butyllithium at —70°C.[398] When the temperature of the reaction mixture is allowed to rise from —70°C to room temperature, there is a general tendency for the initial reaction products to be transformed to a mixture consisting of rearranged and metalated product. Thus 4-bromo-2-thienyllithium (**159**) transforms to a mixture of 2,4-dibromo-5-thienyllithium (**160**) and 3-bromo-2-thienyllithium (**161**). 3-Bromo-4-thienyllithium gives rise to 3-bromo-2-thienyllithium and 3,4-dibromo-2-thienyllithium; 3-thienyllithium changes to 2-thienyllithium and 3-bromo-2-thienyllithium, whereas 3-bromo-2-thienyllithium tends to transform to 2,4-dibromo-5-thienyllithium.[398] The mechanism of these transformations, which ultimately lead to the derivatives in which the lithium occupies the most acidic position, involves a complex series of halogen–metal interconversions and metalations in a series of coupled equilibria. The more important

[396] S. O. Lawesson, *Arkiv Kemi* **11**, 317 (1957).
[397] S. O. Lawesson, *Arkiv Kemi* **11**, 325 (1957).
[398] P. Moses and S. Gronowitz, *Arkiv Kemi* **18**, 119 (1961).
[399] S. O. Lawesson, *Arkiv Kemi* **11**, 337 (1957).
[400] S. Gronowitz, *Arkiv Kemi* **12**, 115 (1958).
[401] E. Campaigne and W. O. Foye, *J. Am. Chem. Soc.* **70**, 3941 (1948).

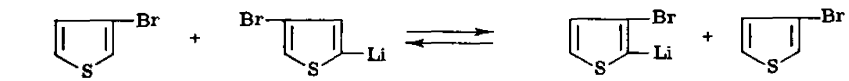
steps in the transformations of 4-bromo-2-thienyllithium are indicated in the reaction schemes of (**159**) to (**161**).



[*159*]



[*160*]



[*161*]

The relative rates of formation of (**160**) and (**161**) are very sensitive to the experimental conditions as 3-bromothiophene has a catalytic effect on the formation of (**161**).

When the bromothiophenes and *n*-butyllithium are reacted at room temperature, halogen–metal interconversion and metalation occur concurrently to different degrees, and mixtures are obtained.[398]

The stability of the *o*-bromothienyllithium reagents at —70°C contrasts sharply with the behavior of *o*-bromophenyllithium which is very unstable even at —100°C, readily splitting off lithium bromide to form benzyne (dehydrobenzene).[402] Only by heating bis-(3-iodo-2-thienyl)mercury to 240°C in the presence of tetracyclone could some evidence for the intermediate existence of 2,3-dehydrothiophene be obtained.[403]

The halogen–metal interconversion has been pictured as an ex-

[402] H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.* **79**, 2625 (1957).
[403] G. Wittig and V. Wahl, *Angew. Chem.* **73**, 492 (1961).

change between lithium and an electropositive halogen atom, and it is supposed that the ease of interconversion is proportional to the degree of positive polarization of the halogens.[404] The facile interconversion of bromothiophenes is, therefore, understandable as the thiophene nucleus both inductively and conjugatively can act as an electron sink, an effect which can be strengthened on demand of the reagent. The effective conjugation of the thienyl group with a +M-substituent, as mentioned before, has been demonstrated by NMR spectroscopy and dipole-moment measurements.

The electropositive nature of the halogens in thiophenes is illustrated by the halogen–metal interconversion between 2,5-dichlorothiophene and *n*-butyllithium.[405] Normally the more electronegative chlorine is exchanged very sluggishly. The differences in reactivity of the halogens is also obvious from the fact that whereas 2-iodo-[401] and 2-bromo-thiophene undergo halogen-metal exchange to give 2-thienyllithium, 2-chlorothiophene is metalated to 2-chloro-5-thienyllithium.[405]

The α-positioned bromine of 2-bromothiophene, 2,3- and 2,4-dibromothiophene, and 2,3,5-tribromothiophene also gives (at room temperature) smooth interconversion with ethyl magnesium bromide, showing the high reactivity of α-halogens in interconversion reactions.[400] Bromobenzenes and β-bromothiophenes[61] do not react under these conditions. Interconversion with magnesium compounds is less selective than with lithium compounds, as a mixture of 87% 2,4-dibromothiophene and 13% 2,3-dibromothiophene was obtained upon hydrolysis of the interconversion product between 2,3,5-tribromothiophene and ethyl magnesium bromide.[400]

The broad spectrum of substitution reactions discussed in the last two sections illustrates the ability of thiophene to adapt itself to the demands of the reagents. It easily undergoes electrophilic substitution which requires the concentration of electrons to the α-position as well as nucleophilic substitution during which electrons are withdrawn from the reacting α-carbon. Halogen atoms easily leave the thiophene molecule either negatively or positively charged, as required by the reagent.

The stability of the bromothienyllithium reagents at −70°C have made them very useful for the preparation of isomer-free 2,3-, 2,4-, and 3,4-disubstituted thiophenes, since bromine atoms of the corresponding dibromothiophenes can be replaced stepwise with other groups via the lithium derivative, provided that the group introduced first does not interfere with the second halogen–metal exchange. Thus, 4-methylthio-3-thiophenealdehyde has been prepared from 3,4-dibromothiophene by stepwise conversion via 3-bromo-4-thienyllithium, 3-bromo-4-methylthiothiophene, and 4-methylthio-3-thienyllithium, the appropriate reagents being *n*-butyllithium, dimethyl disulfide, and *N,N*-dimethylformamide.[44] The same principle has been applied to the synthesis of 2-methylthio-4-thiophenealdehyde and 2-methylthio-3-thiophenealdehyde.[44] Similarly four isomeric methylthiothiophenethiols[65] and four deuterated methylthiothiophenes[240] were prepared by using sulfur and deuterated acetic acid as the second reagents, respectively. Methyl groups are introduced more conveniently in two steps by Wolff-Kishner reduction of the aldehydes[133] than by direct reaction of the lithium derivatives with dimethyl sulfate or methyl-*p*-toluene sulfonate. With these reagents some isomerizations have been noticed.[240] After salt formation, carboxyl groups do not interfere in the halogen-metal exchange,[309,406] and carbonyl groups can be protected through acetal formation before halogen-metal exchange.[304] Other examples of the use of organolithium derivatives for the preparation of disubstituted thiophenes can be found in references 44, 65, and 240. In this way many thiophenes can be prepared which cannot be obtained by direct substitution of monosubstituted thiophenes utilizing the directing effects of substituents (cf. Section IV,B).

The technique of blocking certain reactive positions with easily removable groups, which has been commented upon earlier, has also been applied to the synthesis of disubstituted thiophenes as exemplified by the Imoto *et al.* synthesis of 3-bromo-4-nitrothiophene.[233] Recently Goldfarb *et al.* have introduced the SCH_3 group as a blocking agent, partly because it is removed during Raney nickel desulfurization and partly because it can, after oxidation to the sulfoxide, be cleaved with *n*-butyllithium.[331]

2-Thienyllithium has been used for the preparation of triphenyl-2-thienylsilane,[407] 2-thienylsulfinic acid,[408] and di-2-thienylketone[409] by means of reactions with triphenyl chlorosilane, sulfur dioxide, and

[404] R. G. Jones and H. Gilman, *Org. Reactions* **6**, 339 (1951).
[405] G. B. Bachman and L. W. Heisey, *J. Am. Chem. Soc.* **70**, 2378 (1948).
[406] S. O. Lawesson, *Arkiv Kemi* **11**, 345 (1957).
[407] H. Gilman, R. A. Benkeser, and G. E. Dunn, *J. Am. Chem. Soc.* **72**, 1689 (1950).
[408] W. E. Truce and E. Wellisch, *J. Am. Chem. Soc.* **74**, 5177 (1952).
[409] N. Löfgren and C. Tegnér, *Acta Chem. Scand.* **6**, 1020 (1952).

carbon dioxide, respectively. It adds to the azomethine linkage of pyrimidine giving, upon oxidation with $KMnO_4$, 4-(2-thienyl)pyrimidine.[410]

VI. Side-Chain Reactivity of Thiophenes

A. Applications of the Hammett Equation

The large success of the Hammett equation in relating and systematizing the side-chain reactivities of *meta*- and *para*-substituted benzenes has stimulated similar studies in the thiophene series.

The rate of saponification of ethyl 2-thenoate, in contrast to ethyl 3-thenoate, was found to be considerably slower than predicted from the pK_a of the acid,[411] showing that the reactivities of thiophenes do not parallel those of benzene. The first explanation, that this was produced by a steric effect of the ring sulfur[411] similar to the case in *ortho*-substituted benzenes and in ethyl 1-naphthoate, could not be upheld when the same effect was found in ethyl 2-furoate.[412,413] It was later ascribed to a stereospecific acid strengthening factor, involving the proper relation of the carboxylic hydrogen and the heteroatom, as the rate of saponification of 2-thienylacrylic acid was in agreement with that predicted from the acid constants.[412]

So-called aryl values have been introduced by Imoto *et al.*[414,415] for the purpose of systematizing the reactivities of different aromatic systems by means of the linear free-energy relationship, which however, could not be applied to the decomposition rates of heterocyclic acyl azides in toluene.[416]

From measurements of acid constants,[411,417,418] and rates of esterification[419] of 5-substituted 2-thenoic acids, and from the saponification of substituted methyl[420] and ethyl thenoates,[419] Imoto *et al.*[418,421,422] and Tirouflet *et al.*[420] concluded that substituent constants (σ) and reaction constants (ρ) similar to those for *para*-substituted benzenes can be used. Similar treatment was also indicated by the measured rates of side-chain bromination of 5-substituted 2-acetylthiophenes[419] and of the acetoxymercuration of 2-substituted thiophenes.[252] Similar conclusions have been drawn from a study of half-wave potentials in the polarographic reduction of substituted nitrothiophenes and thiophenealdehydes.[267,420,423-426] Similarly, the reactivities of 4-substituted 2-thenoic acids and their esters can be systematized by using the same ρ- and σ_{meta}-values as in the benzene series.[418,421] This cannot be done, however, with 5-substituted 3-thenoic acids and esters. If σ_{meta} is used, ρ-values larger than for benzenes are obtained for dissociation, and smaller values for hydrolysis.[418,421] The Hammett equation has been found applicable to the spontaneous decomposition of substituted bis(2-thenoyl) peroxides.[426a]

The aforementioned exception and the rather limited experimental material available do not allow any conclusions about the general applicability of the Hammett equation, using the same σ- and ρ-values as for benzenes, to be drawn with certainty. The present author has pointed out that large deviations should be expected with strong +M-substituents,[22] as is also indicated from the rates of alkaline hydrolysis of methyl 5-amino- and 5-acylamino-2-thenoates.[420] From the chemical shifts in the NMR spectra of thiophenes and benzenes[22] it appears that another set of σ-values should be used in the thiophenes series which seems plausible since the transmission of the sub-

[410] H. Bredereck, R. Gompper, and H. Herlinger, *Angew. Chem.* **70**, 571 (1958).
[411] C. C. Price, E. C. Mertz, and J. Wilson, *J. Am. Chem. Soc.* **76**, 5131 (1954).
[412] C. C. Price and E. A. Dudley, *J. Am. Chem. Soc.* **78**, 68 (1956).
[413] S. Oae and C. C. Price, *J. Am. Chem. Soc.* **79**, 2547 (1957).
[414] Y. Otsuji, Y. Kubo, M. Koda, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1300 (1959); *Chem. Abstr.* **55**, 6476 (1961).
[415] Y. Otsuji, M. Kubo, and E. Imoto, *Bull. Univ. Osaka Prefect. Ser. A* **7**, 61 (1960).
[416] Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1307 (1959); *Chem. Abstr.* **55**, 6477 (1961).
[417] E. Imoto and R. Motoyama, *Bull. Naniwa Univ.* **2A**, 127 (1954); *Chem. Abstr.* **49**, 9614 (1955).
[418] E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect. Ser. A* **6**, 115 (1958).

[419] E. Imoto, Y. Otsumi, and T. Hirai, *Nippon Kagaku Zasshi* **77**, 804 (1956); *Chem. Abstr.* **52**, 9066 (1958).
[420] J. Tirouflet and J. P. Chané, *Compt. rend. acad. sci.* **245**, 80 (1957).
[421] Y. Otsuji, T. Kimura, Y. Serugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi* **80**, 1021 (1959); *Chem. Abstr.* **55**, 5467 (1961).
[422] Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1297 (1959); *Chem. Abstr.* **55**, 6476 (1961).
[423] E. Imoto, R. Motoyama, and H. Kakiuchi, *Nippon Kagaku Zasshi* **77**, 812 (1956); *Chem. Abstr.* **52**, 9066 (1958).
[424] E. Imoto, R. Motoyama, and H. Kakiuchi, *Bull. Naniwa Univ.* **A3**, 203 (1955).
[425] J. Nakaya, H. Kinoshita, and S. Ono, *Nippon Kagaku Zasshi* **78**, 935 (1957); *Chem. Abstr.* **53**, 21276 (1959).
[426] J. Tirouflet, *Bull. soc. chim. France* p. 1066 (1958).
[426a] R. D. Schuetz and D. M. Teller, *J. Org. Chem.* **37**, 410 (1962).

stituent effects to different positions and the extent of conjugation should be dependent on the electronic character and geometry of the ring.[22]

The rates of alkaline hydrolysis of ethyl benzoate, ethyl 2-thenoate, and 3-thenoate are very similar. Also, the acid constants of benzoic acid ($pK_a = 4.20$) and 3-thenoic acid ($pK_a = 4.08$) are of the same magnitude, whereas 2-thenoic acid ($pK_a = 3.49$) is stronger.

A comparison of the polarographic reduction of 2- and 3-substituted thiophenes have shown that the 2-isomers are more easily reduced than the 3-isomers.[427] Polarography has also been used for the quantitative study of the dehalogenative reduction of 2-halo-5-carbonyl thiophenes[428] and for the study of the hydroxychalcone–chromanone equilibrium in thienylsubstituted compounds.[429]

B. The Structure and Reactions of Hydroxy-, Amino-, and Mercapto-thiophenes

1. *Hydroxythiophenes*

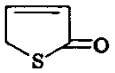
One of the most striking differences between benzene and thiophene chemistry is the instability and difficult accessibility of the thiophene analogs of such important, well-known, and easily available compounds as phenol, aniline, and thiophenol.

2-Thienol was first prepared by Hurd *et al.* through the reaction of 2-thiophene magnesium bromide with oxygen in the presence of isopropyl magnesium bromide,[430] or through the reaction of 2-thienyllithium with 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide[431] in low yield. It is more conveniently prepared in high yield by the acid-catalyzed dealkylation of 2-*t*-butoxythiophene.[432] Substituted thienols have also been prepared by hydrogen peroxide oxidation of thiopheneboronic acids.[432a]

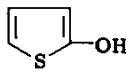
From the presence of bands in the IR-spectra characteristic of the C=O and OH groups, as well as of aliphatic and aromatic C—H stretching frequencies, Hurd *et al.* concluded that 2-thienol was a

[427] J. Tirouflet and E. Laviron, *Comp. rend. acad. sci.* **246**, 274 (1958).
[428] J. Nakaya, H. Kinoshita, and S. Ono, *Nippon Kagaku Zasshi* **80**, 1334 (1959); *Chem. Abstr.* **55**, 4471 (1961).
[429] A. Corvaisier and J. Tirouflet, *Compt. rend. acad. sci.* **251**, 1641 (1960).
[430] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.* **72**, 5543 (1950).
[431] C. D. Hurd and H. J. Anderson, *J. Am. Chem. Soc.* **75**, 5124 (1953).
[432] S. O. Lawesson and C. Frisell, *Arkiv Kemi* **17**, 393 (1961).
[432a] A.-B. Hörnfeldt and S. Gronowitz, *Acta Chem. Scand.* **16**, 789 (1962).

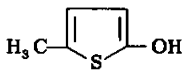
tautomeric mixture.[430] Also, the UV spectra gave indications of the presence of the C=C—C=O system.[430] A study of the NMR spectrum of the liquid compound showed that 2-thienol apparently existed completely as 3-thiolene-2-one (**162**).[53] No lines of the enol form (**163**) could be detected. The discrepancies concerning the properties of the so-called thiotenol (5-methyl-2-hydroxythiophene) (**164**) were clarified by NMR studies.[53] Two tautomeric forms, 5-methyl-4-thiolen-2-one (**165**) and 5-methyl-3-thiolen-2-one (**166**), could be isolated



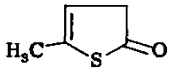
[*162*]



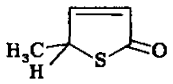
[*163*]



[*164*]



[*165*]



[*166*]

which on standing transformed to a mixture consisting of about 85% of (**166**) and 15% of (**165**).[53] No lines belonging to (**164**) could be detected.

In the absence of oxygen, these thiolene-2-ones are rather stable and have been kept at 0°C for several months. 3-Hydroxythiophene, on the other hand, which has been prepared in low yield from 3-thiophenemagnesium bromide in the same way as the 2-isomer,[433] or through decarboxylation of 3-hydroxy-2-thiophenecarboxylic acid,[159] is very unstable. Its IR spectrum indicates that it also exists as a tautomeric mixture largely in its enolic form.[433]

3,5-Dinitro-2-hydroxythiophene and 3-nitro-5-acetyl-2-hydroxythiophene have been obtained from nitrochlorothiophenes through reaction with sodium formate in methanol.[376] These compounds were colorless crystalline substances which decomposed with evolution of nitrogen oxides and formation of a dark resin even at −20°C. They gave, however, stable, colored, sodium salts, with ionization constants of the

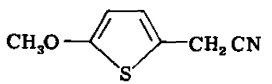
[433] M. C. Ford and D. Mackay, *J. Chem. Soc.* p. 4985 (1956).

order of 10^{-2} and 10^{-3}. The tautomeric structure was not discussed.[376]

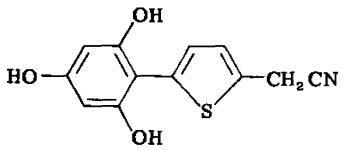
The UV spectrum of 5-phenyl-3-hydroxythiophene is very similar to that of its methyl ether in alcoholic solution, indicating that it exists largely in the enol form in this solvent.[434] The same coincidence of the wavelength maxima was also obtained for 5-phenyl-2-hydroxythiophene and its methyl ether.[434] In chloroform solution, the maxima were shifted toward longer wavelengths, suggesting that the tautomeric equilibrium in this solvent is displaced more toward the "keto form."[434]

The hydroxythiophenes which exist predominantly as the thiolen-2-ones also show reactions characteristic of the enol form. They can be methylated at the oxygen with dimethyl sulfate of diazomethane and they can also be acylated.[376,430,433,434] They also react as thiolene-2-ones showing a reactive methylene group which can be condensed with benzaldehyde.[376,430] The danger of using chemical reactivity data for drawing conclusion as to the physical state of these tautomerizable systems has been pointed out.[53]

The methoxy group of methoxythiophenes shows a reactivity which, in many respects, differs appreciably from the reactivity of the corresponding anisoles. Thus, in an attempted Hoesch synthesis with 5-methoxy-2-thenylcyanide (**167**) and phloroglucinol, the methoxy group reacted instead and 5-(2′,4′,6′-trihydroxyphenyl)-2-thenyl cyanide (**168**) was obtained.[435] 2-Thenyl cyanide reacts normally in the Hoesch synthesis.[436] Likewise, upon acid hydrolysis of the reaction product of 5-methoxy-2-thienyllithium with benzophenone, (**169**) was obtained instead of the expected substituted methoxythiophene.[437] No defined products could be isolated from the attempted Claisen rearrangement of allyl ethers of thiophene to allylsubstituted hydroxythiophenes[379] (cf. also ref. 437a).



[*167*]



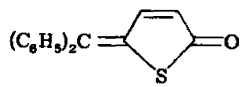
[*168*]

[434] A. I. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Am. Chem. Soc.* **76**, 4450 (1953).

[435] S. Gronowitz and B. Jägersten, *Arkiv Kemi* **18**, 213 (1961).

[436] S. Gronowitz and R. Ekman, *Arkiv Kemi* **17**, 93 (1961).

[437] W. R. Biggerstaff and K. L. Stevens, *138th Meeting, Am. Chem. Soc., New York, 1960,* Abstr., p. 13P.



[*169*]

2. *Aminothiophenes*

Most aminothiophenes are prepared by the reduction of nitrothiophenes. Aminothiophenes or their derivatives have also been obtained through the Hofmann rearrangement of the acid amides, which, however, fails with 2-thenamide, in contrast to the 3-isomer.[319] The Beckmann rearrangement of the oxime of 2-acetylthiophene has been applied successfully to the preparation of 2-acetamidothiophene.[293]

The free aminothiophenes are very unstable compounds and it has not been possible to distil 3-aminothiophene.[319] They are best stored as the stannic-chloride double salts and give stable acetyl derivatives.

The NMR spectra of 2- and 3-aminothiophene showed that they were true amines.[33] No lines belonging to an imino form could be detected. However, from a study of the UV and IR spectra of nitro-substituted aminothiophenes, Hurd and Kreuz concluded that these amines exist as mixtures of amino and imino forms.[376]

The reactivity of the 5-position of 2-aminothiophene in diazo coupling, which is present also in the acylated derivatives,[287,290,319] complicates the formation of a diazonium salt from 2-aminothiophene. Thus Steinkopf and Müller[438] obtained only an azo dyestuff, although they proved, through the isolation of small amounts of 2-thienyl diazonium chloride, the diazotizability of 2-aminothiophene which had earlier been denied. However, recent Russian work claims the preparation of 2-thienyldiazonium chloride by treating the double salt in 10% hydrochloric acid with sodium nitrite.[439] Amazingly high yields (over 90%) of azo compounds were then achieved by coupling the diazonium salt solution with β-naphtol, *m*-toluidine or with the 2-aminothiophene double salt.[439] These authors have also studied the

[437a] W. Herz and L. Tsai, *J. Am. Chem. Soc.* **77**, 3529 (1955).

[438] W. Steinkopf and P. J. Müller, *Ann. Chem. Liebigs* **448**, 210 (1926).

[439] N. I. Putohkin and V. I. Yakovlev, *Doklady Akad. Nauk. S.S.S.R.* **98**, 89 (1954); *Chem. Abstr.* **49**, 12431 (1955).

diazotization of the 2,4-diaminothiophene stannic-chloride double salt and obtained a bis-diazotized product which they coupled with various reagents.[440]

In —I—M-substituted aminothiophenes, the possibility of coupling during diazotization is eliminated. Thus ethyl 5-amino-2-thiophenecarboxylate[441] and 5-amino-2-thiophenesulfonic acid[288] and its amide[291] have been diazotized and coupled with various reagents.

Condensed thienopyridines have been prepared by reacting the stannic-chloride double salts of 2- and 3-aminothiophene with methyl vinyl ketone in the presence of $FeCl_3$ and $ZnCl_2$.[442] Additional rings are also formed in the reaction of the double salt of 3,4-diaminothiophene with oxalic acid or benzil.[443]

3. *Mercaptothiophenes*

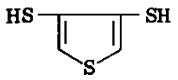
Thiophenethiols are prepared by reduction of the sulfonyl chlorides[444] or, more conveniently, by the reaction of Grignard reagents[444,445] or thienyllithium compounds[64,65] with sulfur. They have also been obtained by cleavage or thienyl alkyl sulfides with sodium in liquid ammonia.[446] 3-Thiophenethiol is a by-product in the commercial thiophene synthesis.[445] Thiophenethiols have recently also been prepared by a synthesis involving Friedel-Crafts reaction of 2,4-dinitrobenzenesulfenyl chloride with thiophenes, followed by basic cleavage of the resulting sulfide.[446a]

The thiophenethiols are rather unstable and polymerize on standing. Especially unstable are bromosubstituted thiophenethiols which decompose violently with formation of a black tar and evolution of hydrogen sulfide and hydrogen bromide.[65]

IR spectra[65] (SH-stretching 3.94–3.99 μ) and NMR spectra[33,34] of 2- and 3-thiophenethiol and of ten monosubstituted thiophenethiols showed that these compounds exist in the thiol forms.

[440] N. I. Putohkin and A. N. Sorokin, *Sbornik Nauch. Trudov., Kuibyshev. Ind. Inst. im. V. V. Kuibysheva* p. 261 (1955); *Chem. Abstr.* **51**, 16419 (1957).
[441] O. Dann, *Chem. Ber.* **82**, 72 (1949).
[442] V. G. Zhiryakov and P. I. Abramenko, *Zhur. Vsesoyuz. Khim. Obshchestva im D. I. Mendeleeva* **5**, 707 (1960). *Chem. Abstr.* **55**, 11416 (1961).
[443] R. Motoyama and E. Imoto, *Nippon Kagaku Zasshi* **78**, 793 (1957); *Chem. Abstr.* **54**, 22560 (1960).
[444] W. H. Houff and R. D. Schuetz, *J. Am. Chem. Soc.* **75**, 6316 (1953).
[445] P. D. Caesar and P. D. Branton, *Ind. Eng. Chem.* **44**, 122 (1952).
[446] Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *Proc. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 1572 (1960).
[446a] R. D. Schuetz and W. L. Fredericks, *J. Org. Chem.* **27**, 1301 (1962).

3,4-Thiophenedithiol (**170**) has been prepared by halogen–metal interconversion between the lithium salt of 4-bromo-3-thiophenethiol and *n*-butyllithium at −70°C, followed by reaction with sulfur.[447] IR, NMR, and UV spectra showed that this compound exists in the dithiol form (**170**).[447] The compound obtained as a by-product in the



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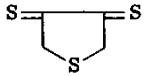
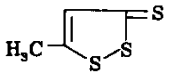


[*171*]

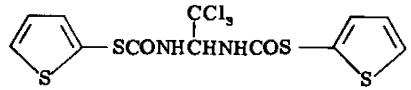


[*172*]

commercial thiophene synthesis from butane and sulfur and described as 3,4-thiolanedithione (**171**)[445] [viz., the tautomeric dithione form of (**170**)] is 5-methyl-1,2-dithiole-3-thione (**172**).[447]

The alkali salts of thiophenethiols react normally with aliphatic halogen compounds to give sulfides[351–355,444,448–449a] and have also been added to the double bond of vinyl pyridines.[450] With aromatic diazonium salt, aryl sulfides have been obtained.[284] With bromocyanogen, the sodium salt of 3-thiophenethiol gives 3-thiocyanothiophene in low yield, the main product being di-3-thienyl disulfide.[64] The reaction of 2-thienylthiolate with phenyl sulfenyl chloride and the reaction of 2-thienylsulfenyl chloride with 2-pyridinethione has been utilized for the preparation of unsymmetrical disulfides.[451]

The correct structure of the condensation product of 2-thiocyanothiophene and chloral in the presence of sulfuric acid is (**173**).[452]



[*173*]

[447] S. Gronowitz and P. Moses, *Acta Chem. Scand.* **16**, 105 (1962).
[448] J. W. Brooks, E. G. Howard, and J. J. Wehrle, *J. Am. Chem. Soc.* **72**, 1289 (1950).
[449] W. H. Houff and R. D. Schuetz, *J. Am. Chem. Soc.* **75**, 2072 (1953).
[449a] R. W. Higgins and R. Garret, *J. Org. Chem.* **27**, 2168 (1962).
[450] E. Profft, *Monatsber. deut. Akad. Wiss. Berlin* **1**, 694 (1959).
[451] F. Runge, A. Jumar, and P. Held, *J. prakt. Chem.* **280**, 44 (1959).
[452] R. Riemschneider, *Monatsh. Chem.* **84**, 883 (1953).

C. The Reactivity of Thenyl Derivatives

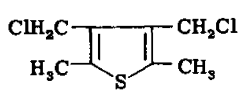
2-Thenyl halides are prepared through chloromethylation (cf. Section III,C) or through side-chain bromination of methylthiophenes with *N*-bromosuccinimide.[221,222,317,453-458] More reproducible results are obtained with the latter method when the reactive ring positions are blocked[236,453-456] or deactivated by —I—M-substituents.[457] Thus 3-nitro-2-methylthiophene can be both mono- and di-brominated in the methyl group.[457] In contrast to the reactivity of 3-nitro-2-methyl thiophene, 3-methyl-2-nitrothiophene was unaffected by *N*-bromosuccinimide in boiling CCl_4. However, in boiling ethylene dibromide side-chain bromination could be obtained.[457]

The thenyl chlorides appear to be more reactive in nucleophilic aliphatic substitution than the benzyl analogs. Thus, 2-thenyl chloride gives, in the reaction with sodium cyanide in ethanol, a mixture of ethyl 2-thenyl ether (25% yield) and 2-thenyl cyanide (32% yield),[459,460] whereas benzyl chloride gives a high yield of benzyl cyanide uncontaminated with benzyl ether. When 2-thenyl chloride and benzyl chloride were allowed to compete for a deficiency of sodium amyloxide, 2-thenyl chloride reacted three times faster.[459] In acetone solution 2-thenyl cyanide is obtained smoothly.[460]

The reactivity of the chloromethyl group is illustrated by the reaction of 2,5-dimethyl-3,4-dichloromethylthiophene (**174**) with water, which gives (**175**).[461] Another example of ether formation, is the formation of (**176**) upon normal acidic workup of the reaction product from 2-thiophenemagnesium bromide and 2-thiophenaldehyde.[462] With

[453] E. Campaigne and W. Le Suer, *J. Am. Chem. Soc.* **71**, 333 (1949).
[454] K. D. Dittmer, R. P. Martin, W. Herz, and S. J. Cristol, *J. Am. Chem. Soc.* **71**, 1201 (1949).
[455] T. W. Campbell and W. W. Kaeding, *J. Am. Chem. Soc.* **73**, 4018 (1951).
[456] E. Campaigne, P. A. Monroe, B. Arnwine, and W. L. Archer, *J. Am. Chem. Soc.* **75**, 988 (1953).
[457] H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.* **79**, 2556 (1957).
[458] M. Neeman, E. Krakauer, and Y. Shorr, *J. Am. Chem. Soc.* **79**, 4380 (1957).
[459] T. L. Cairns and B. C. McKusick, *J. Org. Chem.* **15**, 790 (1950).
[460] K. Pettersson, *Acta Chem. Scand.* **4**, 395 (1950).
[461] Ya. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 1235 (1956).
[462] Ya. L. Goldfarb and M L. Kirmalova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 759 (1956).

ammonium chloride the benzhydrol analog is obtained in good yield.[462] Resinification often occurs on hydrolysis of thenyl chlorides with sodium hydroxide or acetate and is best achieved by reaction with



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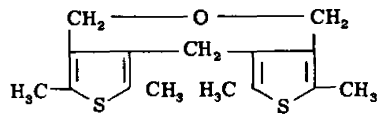
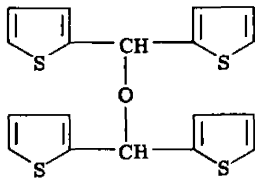


[*175*]



[*176*]

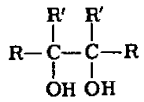
sodium formate and hydrolysis of the formyl ester with hydrochloric acid.[280]

The high reactivity of 2-thenyl halides has been ascribed to the ability of the thiophene nucleus to conjugate more effectively than the phenyl ring[21] with the *p*-orbital of the α-carbon during nucleophilic aliphatic substitution. It is known that nucleophilic aliphatic substitution in benzyl halides is strongly accelerated by conjugatively electron-donating groups such as OCH_3 in the *para* position and strongly retarded by electron-attracting groups such as NO_2 in the same position.[463] Although the —I effect of the 2-thienyl is stronger than that of the phenyl group and should retard the reaction, it is obvious that the conjugatively electron-donating effect which is strengthened during the reaction is responsible for the increased reactivity in 2-thenyl chlorides.[21]

A study of the rearrangement of pinacols of the general type (**177**) has elegantly demonstrated the capacity of the thienyl group to supply

[463] Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.* **79**, 1909 (1957).

electrons; this facilitates its migration to the adjacent positive cen-



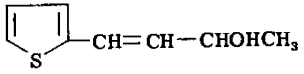
[177]

ter.[464,465] It was found that when R = 2-thienyl and R′ = phenyl, only the 2-thienyl group migrated.[464] This was also the case for R = 2,5-dimethyl-3-thienyl.[464] From the rearrangement of 1,2-di-(2-thienyl)-1,2-di-(4-methoxyphenyl)ethane-1,2-diol (**177**, R = 2-thienyl, R′ = 4-methoxyphenyl), it was found that the migratory aptitude of 2-thienyl was twice that of *p*-methoxyphenyl and thus one thousand times that of phenyl.[465] The migratory aptitude of 2-furyl was even greater.[465]

The three pinacols were prepared by reducing phenyl-2-thienyl ketone with zinc and acetic acid,[464] by the reaction of 2,5-dimethyl-3-thienylmagnesium iodide with benzil and by the reaction of 2-thienylmagnesium bromide with anisil.[465]

Quantitative measurements of the rate of acid catalyzed rearrangement of 3-methyl-1-(2-thienyl)allyl alcohol (**178**) to 1-methyl-3-(2-thienyl)allyl alcohol (**179**) showed that (**178**) rearranged forty times faster than the phenyl analog but about three times slower than the

[178]



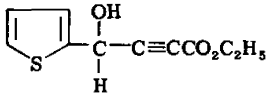
[179]

p-methoxyphenyl analog.[466] It is well established that acid-catalyzed anionotropy is facilitated by electron-donating substituents.[466]

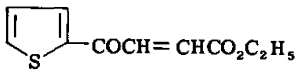
On the other hand, the electron-attracting properties (—I and —M) of the 2-thienyl groups should also facilitate prototropic reactions,[21] where the rate-determining step is the removal of a proton from the α-carbon and which thus is facilitated by electron-attracting sub-

[464] M. R. Kegelman and E. V. Brown, *J. Am. Chem. Soc.* **75**, 5961 (1953).
[465] M. R. Kegelman and E. V. Brown, *J. Am. Chem. Soc.* **76**, 2711 (1954).
[466] E. A. Braude and J. S. Fawcett, *J. Chem. Soc.* p. 4158 (1952).

stituents in the phenyl group. This has been found to be the case through a quantitative study of the base-catalyzed racemization of phenyl and thienylsubstituted glycolic acids.[116] It was found that 2-thienylglycolic acid was racemized thirty-three times faster than mandelic acid and twenty times faster than the 3-isomer.[116] In the presence of a tertiary amine, ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate (**180**) easily undergoes prototropic rearrangement to *trans*-β-2-thenoyl acrylate (**181**).[467]



[180]



[181]

It is thus obvious that the 2-thienyl group is both a better electron donator and electron acceptor than the phenyl group, facilitating both nucleophilic and prototropic reactions at the α-methylene carbon.

Thenyl halides are of great importance for the preparation of aldehydes via the Sommelet reaction.[453,456] The mechanism of this reaction suggested by Hartough and Dickert[468] has been shown to be erroneous.[469] Through a detailed study Angyal *et al.* found experimental conditions which gave a considerably higher yield in the hydrolysis of the hexamine salts.[469] The methylene derivatives of 2-thenylamine, which play an important role both in the Sommelet reaction and in the aminomethylation of thiophene, have been shown to be trimeric[469] and not dimeric.[468] The mechanism of these reactions is essentially a hydrogenation–dehydrogenation process in which the monomer methylenamine is hydrogenated at the expense of an amine.[469]

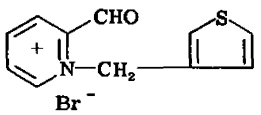
The Sommelet reaction failed with 5-nitro-2-thenyl bromide.[470] 5-Nitro-2-thiophenealdehyde is, therefore, best obtained by nitration of 2-thiophenealdehyde diacetate and separation of the 5-isomer.[471,472]

[467] A. Vaitiekunas and F. F. Nord, *J. Am. Chem. Soc.* **76**, 2737 (1954).
[468] H. D. Hartough and J. J. Dickert, *J. Am. Chem. Soc.* **71**, 3922 (1949).
[469] S. J Angyal, D. R. Penman, and G. P. Warwick, *J. Chem. Soc.* p. 1742 (1953).
[470] M. E. Dullaghan, L. J. Owen, and F. F. Nord, *J. Am. Chem. Soc.* **74**, 2676 (1952).
[471] T. Patrick and W. Emerson, *J. Am. Chem. Soc.* **74**, 1356 (1952).
[472] V. M. Zubarovskii, *Doklady Akad. Nauk S.S.S.R.* **83**, 85 (1952); *Chem. Abstr.* **47**, 2166 (1953).

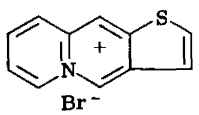
Aldehydes are also obtained from thenylalcohols by oxidation with selenium dioxide,[457,470] *N*-bromosuccinimide,[457] persulfate,[473] lead dioxide, and nitric acid.[317]

The Grignard reagent from 2-thenyl chloride can be obtained by the use of the "cyclic reactor."[474,475] However, rearrangement occurs in its reaction with carbon dioxide, ethyl chlorocarbonate, acetyl chloride, formaldehyde, and ethylene oxide to 3-substituted 2-methylthiophenes.[475] Only in the case of carbon dioxide has the normal product also been isolated.

3-Thenyl bromide and 2-pyridinealdehyde reacted to form a quaternary salt (**182**) which was cyclodehydrated to thieno(2,3-*b*)quinazolinium bromide (**183**).[458]



[*182*]



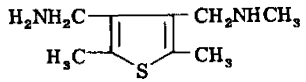
[*183*]

Dehydration to 2-vinylthiophene is better achieved from 2-(2-thienyl)ethanol with powdered potassium hydroxide in the presence of copper than from 1-(2-thienyl)ethanol.[476] α-Chloro-2-thienylpropane undergoes a Wurtz reaction with active iron to give 3,4-di-(2-thienyl)hexane in low yield,[477] which has also been obtained through coupling with *n*-butyllithium.[478]

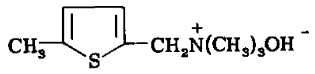
The reduction of diphenyl-2-thienylchloromethane gave the stable hexasubstituted ethane which shows no tendency to dissociate into radicals.[479] The diphenyl 2-thienylmethyl cation was formed during the reduction.

[473] Z. Horii, K. Sakurai, K. Tomino, and T. Konishi, *Yakugaku Zasshi* **76**, 1101 (1956); *Chem. Abstr.* **51**, 3553 (1957).
[474] R. Gaertner, *J. Am. Chem. Soc.* **72**, 4326 (1950).
[475] R. Gaertner, *J. Am. Chem. Soc.* **73**, 3934 (1951).
[476] I. V. Andreeva and M. M. Koton, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **27**, 1079 (1957).
[477] N. P. Buu-Hoi and D. Lavit, *Bull. soc. chim. France* p. 292 (1958).
[478] J. Sicé and M. Mednick, *J. Am. Chem. Soc.* **75**, 1628 (1953).
[479] T. L. Chu and T. J. Weismann, *J. Am. Chem. Soc.* **77**, 2189 (1955).

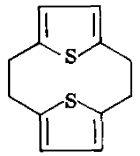
The reactions of (**174**) with various amines has been studied.[480,481] Hydrolysis of the hexamine salt of (**174**) gave not the symmetric diamine but (**184**) via a cyclic intermediate.[480] The pyrolysis of 5-methyl-2-thenyltrimethyl ammonium hydroxide (**185**) is claimed to give (**186**) throught a 1,6 Hofmann elimination reaction.[482] The Bischler-Napieralski cyclization has been applied to acetyl derivatives of 2-(2-thienyl)ethylamine and 2-(3-thienyl)ethylamine for the preparation of sulfur analogs of isoquinoline.[483]



[*184*]



[*185*]



[*186*]

The thenyl cyanides are of great importance for the preparation of thiophene derivatives. Because of the acidifying effects of both the thienyl and of the cyano groups, carbanions are easily obtained through the reaction with sodamide[460,484] or sodium ethoxide,[484,485] which can be alkylated with halides,[484] carbethoxylated with ethyl carbonate,[460,484,485] or acylated by Claisen condensation with ethyl

[480] M. S. Kondakova and Ya. L. Goldfarb, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 570 (1958).
[481] Ya. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Engl. Transl.*) p. 501 (1961).
[482] H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.* **82**, 1428 (1960).
[483] W. Herz, *J. Am. Chem. Soc.* **73**, 351 (1951).
[484] F. Leonard and L. Simet, *J. Am. Chem. Soc.* **74**, 3218 (1952).
[485] K. Pettersson, *Acta Chem. Scand.* **7**, 1311 (1953).

propionate.[486] The β-ketonitrile obtained in the last-mentioned reaction was used for the preparation of antiparasitic thienylsubstituted 2,4-diaminopyrimidines.[486] The β-cyanoesters obtained upon carbethoxylation can be alkylated directly with benzyl chloride or 2-thenyl chloride in the presence of anhydrous potassium carbonate.[460,487,488] 2-Thenyl cyanide has been condensed with aromatic aldehydes to acrylonitriles through the use of catalytic amounts of aqueous potassium hydroxide.[489]

D. Carbonyl Group Reactivities in Thiophenes

The carbonyl group reactivities in thiophenes and benzenes are very similar, as shown by the similar rates of alkaline hydrolysis of esters and by the great similarity of the thiophenealdehydes to benzaldehyde in numerous carbonyl group reactions. This has been ascribed to the counteracting —I+M effects of the thienyl group in this kind of reactions.[21]

Thiophenealdehydes have been condensed with aliphatic aldehydes,[381,490] methyl ketones,[491-496a] cyclic ketones,[492,497-499] benzyl cyanides,[211,500,501] and aliphatic nitro compounds[223,381] to the corresponding vinylthiophenes. By the use of potassium methylate, 2-thiophenealdehyde has been condensed with the reactive methyl groups of *N*-heterocyclic compounds.[502] Thiophenealdehydes have been condensed with rhodanine[221,436,503,504] for the preparation of mildew-preventing compounds[504] and as intermediates for the synthesis of thenyl cyanides.[436] Thienylsubstituted hydantoins have been obtained from thiophene aldehydes and ketones by different methods.[238,505] The azlactone synthesis has been used for the preparation of 3-nitro-2-thienylpyruvic acid from 3-nitro-2-thiophenealdehyde.[457] The addition of potassium cyanide to the unsaturated condensation products in the Knoevenagel condensation of thiophenealdehydes with ethyl malonate[113,236] or malonic acid[492] has been used for the preparation of thienylsuccinic acids.[113,236] 3-(2-Thienyl)acrylic acid has been prepared by the condensation of 2-thiophenealdehyde with tetraacetoxysilanes in the presence of potassium acetate.[506] β-Amino acids of the thiophene series have been obtained by the reaction of aldehydes with malonic acid in the presence of alcoholic ammonia.[507,508] Via the condensation of 2-thiophenealdehyde with 2,5-piperazinedione, a convenient method for the preparation of 3-(2-thienyl)alanine has been worked out.[509] The condensation of thiophenealdehydes with dihydromuconic acid or 1,6-hexadiine-2,4-dicarboxylic acid, using acetic anhydride and lead dioxide, gives α,ω-dithienyl polyenes.[510] A substituted bisphenol has been obtained from the condensation of 2-thiophenealdehyde with 6-*t*-butyl-*m*-cresol.[511]

Schiff bases are obtained through the reaction with aniline.[512,513] In contrast to furfural anil, 2-thiophenealdehyde anil does not react further with aniline hydrochloride.[512] The reaction of 2-thiophenealde-

[486] E. F. Rogers, W. J. Leanza, and L. H. Sarett, *J. Org. Chem.* **22**, 1492 (1957).
[487] A. Fredga and K. Pettersson, *Acta Chem. Scand* **4**, 1306 (1950).
[488] K. Pettersson, *Acta Chem. Scand.* **4**, 1319 (1950).
[489] N. P. Buu-Hoi, N. Hoan, and D. Lavit, *J. Chem. Soc.* p. 485 (1953).
[490] G. Carrara, R. Ettore, F. Fava, G. Roland, E. Testa, and A. Vecchi, *J. Am. Chem. Soc.* **76**, 4391 (1954).
[491] W. L. Nobles, *J. Am. Chem. Soc.* **77**, 6675 (1955).
[492] M. Lj. Mihailović and M. Tot, *J. Org. Chem.* **22**, 652 (1957).
[493] G. A. Hanson, *Bull. soc. chim. Belges* **67**, 712 (1958).
[494] J. Tirouflet and A. Corvaisier, *Compt. rend. acad. sci.* **250**, 1276 (1960).
[495] N. P. Buu-Hoi, N. D. Xuong, and M. Sy, *Bull. soc. chim. France* p. 1646 (1956).
[496] G. Pappalardo, *Gazz. chim. ital.* **89**, 1736 (1959).
[496a] N. P. Buu-Hoi, N. D. Xuong, and T. C. Trieu, *Bull. soc. chim. France* p. 584 (1961).
[497] R. Pallaud and F. Delaveau, *Compt. rend. acad. sci.* **237**, 1254 (1953).
[498] R. Pallaud and F. Delaveau, *Bull. soc. chim. France* p. 1220 (1955).
[499] N. P. Buu-Hoi and N. D. Xuong, *Compt. rend. acad. sci.* **251**, 2725 (1960).
[500] E. R. Lavagnino and E. R. Shepard, *J. Org. Chem.* **22**, 457 (1957).
[501] N. P. Buu-Hoi and N. D. Xuong, *Bull. soc. chim. France* p. 650 (1957).
[502] W. Ried and S. Hinsching, *Ann. Chem. Liebigs* **600**, 47 (1956).
[503] F. C. Brown, C. K. Bradsher, S. S. Bond, and M. Potter, *J. Am. Chem. Soc.* **73**, 2357 (1951).
[504] F. C. Brown, C. K. Bradsher, S. M. Bond, and R. J. Grantham, *Ind. Eng. Chem.* **46**, 1508 (1954).
[505] J. J. Spurlock, *J. Am. Chem. Soc.* **75**, 1115 (1953).
[506] Yu. K. Yur'ev, G. B. Elyakov, and A. N. Vysokov, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **28**, 1603 (1958).
[507] V. P. Mamaev, N. N. Suworov, and E. M. Rokhlin, *Doklady Akad. Nauk S.S.S.R.* **101**, 269 (1955); *Chem. Abstr.* **50**, 3387 (1956).
[508] V. P. Mamaev and T. D. Rubina, *J. Gen. Chem. S.S.S.R.* (*Eng. Transl.*) **27**, 525 (1957).
[509] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 89 (1958).
[510] R. E. Miller and F. F. Nord, *J. Org. Chem.* **16**, 1380 (1951).
[511] D. J. Beaver and P. J. Stoffel, *J. Am. Chem. Soc.* **74**, 3410 (1952).
[512] R. W. Drisko and H. McKennis, *J. Am. Chem. Soc.* **74**, 2626 (1952).
[513] N. P. Buu-Hoi, T. B. Loc, and N. D. Xuong, *Bull. soc. chim. France* p. 1710 (1956).

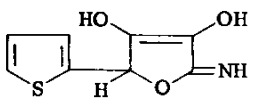
hyde with ammonia and α-mercapto ketones leads to 2-thienylsubstituted thiazolines, which can be dehydrogenated to thienylsubstituted thiazoles.[514] The condensation with *N*-β-mercaptoethylanilines leads to 2-(2-thienyl)-3-aryl thiazolidines.[515]

Also, 3-thiophenealdehyde reacts smoothly in the benzoin condensation[221] and gives, upon mixed benzoin condensation with benzaldehyde, phenyl 3-thenoyl carbinol.[228] The thenils obtained upon oxidation undergo the benzil rearrangement smoothly.[228] Only 3-thienylglycolic acid can be obtained in low yield by the hydrolysis of the corresponding cyanhydrin—the 2-isomer decomposes.[228] Both isomeric thienylglycolic acids are, however, obtained in high yield through base-catalyzed rearrangement of the thienyl glyoxals, obtained through selenium dioxide oxidation of the acetylthiophenes.[62] α-Methoxy-2-thienylacetic acid has been obtained from the base-catalyzed condensation of 2-thiophenealdehyde with chloroform or bromoform in methanol.[516] The isomeric α-methoxythienylacetic acids are obtained easier and in much better yields, however, through the reaction of trichloromethyl thienyl carbinols and methanolic potassium hydroxide.[517] The latter compounds are prepared through the reaction of thienyllithium derivatives or Grignard reagents with chloral.[517,518] The 2-isomer has been hydrolyzed with potassium carbonate to 2-thiophenealdehyde, which is of no preparative importance.[519] The cyanide-catalyzed reaction of 2-thiophenealdehyde with glyoxal leads to **(187)** or **(188)**, depending upon the relative amounts of aldehyde.[520]

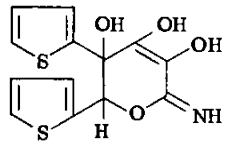
Thiophenealdehydes (unless 5-alkoxysubstituted[276]) undergo the Cannizzaro reaction normally.[133,281] They have been oxidized to acids with silver oxide and sodium bichromate,[233] and can be reduced to the carbinols with the modern metal hydride reagents.

The primary condensation product of 2-thiophenealdehyde with 2 moles of ethyl acetoacetate **(189)** has been cleaved with alkali to

[514] F. Asinger, M. Thiel, W. Dathe, O. Hampel, E. Mittag, E. Plaschil, and C. Schröder, *Ann. Chem. Liebigs* **639**, 146 (1961).
[515] Yu. K. Yur'ev and S. V. Diatlovitskaya, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **28**, 2413 (1958).
[516] W. Reeve and E. L. Compere, *J. Am. Chem. Soc.* **83**, 2755 (1961).
[517] S. Gronowitz and T. Raznikiewicz, *Arkiv Kemi* **17**, 561 (1961).
[518] R. C. Blinn, F. A. Gunther, and R. L. Metcalf, *J. Am. Chem. Soc.* **76**, 37 (1954).
[519] G. Combes, *Bull. soc. chim. France* p. 701 (1952).
[520] H. Dahn, L. Loewe, and H. Hauth, *Helv. Chim. Acta* **40**, 1521 (1957).

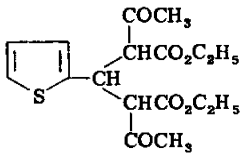


[*187*]

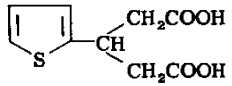


[*188*]

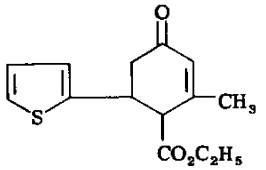
β-(2-thienyl)glutaric acid **(190)**[521] and has also been cyclisized to a cyclohexene derivative **(191)**, by an internal aldol condensation.[522]



[*189*]



[*190*]



[*191*]

The base-catalyzed condensation of 2-thiophenealdehyde with dialkyl phosphorous acid leads to α-(2-thienyl)phosphinic acid.[523]

In connection with the study of tuberculostatic compounds, numerous thiosemicarbazones of thiophenealdehydes[211,456,491,495,524-526] and

[521] W. T. Smith and R. W. Shelton, *J. Am. Chem. Soc.* **76**, 2731 (1954).
[522] K. H. Segel, *Chem. Ber.* **93**, 2529 (1960).
[523] V. S. Abramov and A. S. Kapustina, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **27**, 193 (1957).
[524] N. P. Buu-Hoi, N. D. Xuong, R. Royer, and D. Lavit, *J. Chem. Soc.* p. 547 (1953).
[525] N. H. Nam, N. P. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.* p. 1690 (1954).
[526] N. P. Buu-Hoi, D. Lavit, and N. D. Xuong, *J. Chem. Soc.* p. 1581 (1955).

hydrazides derived from thiophene carboxylic acids[527-529] have been prepared. Thiosemicarbazones were also prepared from 2-thienylpyruvic acids and 2-thienylglyoxal, which were ring closed to 1,2,4-triazines.[530,531]

The carbanions derived from acylthiophenes have been condensed with aldehydes,[493,494,532-534] and, through the Claisen condensation with esters, thienylsubstituted β-diketones have been obtained.[535] 2-Thenoyl trifluoroacetone, first prepared by Reid and Calvin[536] through the Claisen condensation of 2-acetylthiophene with ethyl trifluoracetate, has become an extremely useful chelating agent for the extraction of numerous elements from strongly acidic solutions.[537-545] The tautomeric form which dominates in aqueous solution is the ketone hydrate.[537] Other thiophenes have also proved useful for analytical purposes.[546,547]

The reactive grouping in 2-thienylsubstituted β-diketones has been utilized for the preparation of thienylpyrazoles[548] and 3-(2-thenoyl)-

[527] N. P. Buu-Hoi, N. D. Xuong, N. H. Nam, F. Binon, and R. Royer, *J. Chem. Soc.* p. 1358 (1953).
[528] H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.* **75**, 1933 (1953).
[529] G. Carrara, F. M. Chiancone, V. D'Amato, E. Ginoulhiac, C. Martinúzzi, U. M. Teotino, and N. Visconti, *Gazz. chim. ital.* **82**, 652 (1952).
[530] S. Rossi, *Gazz. chim. ital.* **83**, 133 (1953).
[531] R. E. Hagenbach, E. Hodel, and H. Gysin, *Angew. Chem.* **66**, 359 (1954).
[532] C. S. Marvel, J. M. Quinn, and J. S. Showell, *J. Org. Chem.* **18**, 1730 (1953)
[533] M. Sy, *Inds. parfum.* **12**, 351 (1957). *Chem. Abstr.* **52**, 5752 (1958).
[534] W. Ried and W. Marx, *Chem. Ber.* **90**, 2683 (1957).
[535] L. B. Barkley and R. Levine, *J. Am. Chem. Soc.* **73**, 4625 (1951).
[536] J. C. Reid and M. Calvin, *J. Am. Chem. Soc.* **72**, 2948 (1950).
[537] E. H. Cook and R. W. Taft, Jr., *J. Am. Chem. Soc.* **74**, 6103 (1952).
[538] W. W. Meinke and R. E. Andersson, *Anal. Chem.* **24**, 708 (1952).
[539] P. J. Elving and P. G. Grodzka, *Anal. Chem.* **31**, 2 (1961).
[540] D. M. Hercules, *Talanta* **8**, 485 (1961).
[541] S. F. Marsh, W. J. Maeck, G. L. Booman, and J. E. Rein, *Anal. Chem.* **33**, 870 (1961).
[542] T. C. Rains, M. Ferguson, and H. P. House, *Anal. Chem.* **33**, 1645 (1961).
[543] L. Newman and P. Kutz, *J. Phys. Chem.* **65**, 796 (1961).
[544] A. M. Poskanzer and B. M. Foreman, *J. Inorg. & Nuclear Chem.* **16**, 323 (1961).
[545] K. M. Abubacker and N. S. K. Prasad, *J. Inorg. & Nuclear Chem.* **16**, 296 (1961).
[546] S. G. Tandon and S. C. Bhattacharyya, *Anal. Chem.* **33**, 1267 (1961).
[547] S. G. Tandon, *J. Phys. Chem.* **65**, 1644 (1961).
[548] V. Parrini, *Ann. chim. (Rome)* **47**, 929 (1957).

coumarins[549] through the reaction with hydrazine and substituted *o*-hydroxybenzaldehydes, respectively.

Through careful studies of the experimental conditions, it has become possible to apply the Willgerodt reaction to the synthesis of thienylacetic acids from acetylthiophenes.[550-552]

The Pfitzinger reaction consisting in the alkaline condensation of isatin or 5-bromoisatin with ketones has been applied extensively by Buu-Hoi *et al.*[211,279,310,316,525,553] and by Cagniant,[278,347] to acetylthiophenes. The 2-thienylsubstituted cinchonic acids obtained have been decarboxylated to give 2-thienylsubstituted quinolines.[553] The Fischer indole synthesis has been applied to 5-ethyl-2-acetylthiophene.[279]

The Reformatsky reaction between 2- and 3-thiophenealdehydes and 2- and 3-alkyl thienyl ketones with α-bromoesters has been studied in order to correlate yields with steric factors, reaction solvents, and inductive effects.[554] 3-Substituted compounds gave somewhat higher yields. The α-hydroxyesters obtained could be smoothly dehydrated by refluxing with 6% oxalic acid solution.[554] The Reformatsky reaction between thienyl carbonyl derivatives and ethyl γ-bromocrotonate, allyl, and propargyl bromide has also been investigated.[555] 2-Thiophenealdehydes react normally with Grignard reagents to give alkyl thienyl carbinols which display choleretic activity in rats.[556]

The reaction of benzylmagnesium chlorides with thiophenealdehydes and thienyl ketones has been used for the preparation of styrylthiophenes[525] and 1,2,2-triarylethylenes,[557,558] which are of biological interest. In stilbene and 1,2,2-triphenylethylene the reactivity toward electrophilic reagents is transferred with deactivation to the double bond. However, styrylthiophene is formylated and acylated

[549] N. P. Buu-Hoi, T. B. Loc, and N. D. Xuong, *Bull. soc. chim. France* p. 561 (1957).
[550] O. Dann and H. Distler, *Chem. Ber.* **84**, 423 (1951).
[551] J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.* **73**, 2779 (1951).
[552] J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.* **74**, 1066 (1952).
[553] N. P. Buu-Hoi, R. Royer, N. D. Xuong, and P. Jacquignon, *J. Org. Chem.* **18**, 1209 (1953).
[554] R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.* **77**, 1836 (1955).
[555] R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.* **77**, 1839 (1955).
[556] N. P. Buu-Hoi, N. D. Xuong, and B. K. Diep, *J. Org. Chem.* **26**, 1673 (1961).
[557] N. P. Buu-Hoi, E. Lescot, and N. D. Xuong, *J. Org. Chem.* **22**, 1057 (1957).
[558] N. P. Buu-Hoi, E. Lescot, and N. D. Xuong, *J. Org. Chem.* **23**, 1261 (1958).

in the thiophene α-position, illustrating the higher reactivity of thiophene in electrophilic substitution.[525] Upon bromination only a dibrominated compound could be isolated which was substituted both in the ring and at the double bond.[525,558]

The Leuckart synthesis has been applied successfully in the thiophene series. *N,N*-Dimethyl thenylamine and *N,N*-diethyl thenylamine were obtained from 2-thiophenealdehyde and the appropriate formamide.[559] Seven α-(2-thienyl)-β-arylethylamine hydrochlorides have been prepared from the corresponding ketones in about 40–60% yields[560] and, finally, *N*-methyl-1-(3-thienyl)-2-propylamine was obtained in 48% yield in the Leuckart reaction from 3-thienylacetone, methylamine, and formic acid.[223]

2-Thiophenealdehyde has been used in the reductive alkylation of 2-aminopyridine and 2-aminopyrimidine.[561] 2-Arylamino-4-(2-thienyl)thiazoles have been prepared by the reaction of 2-acetylthiophene with *N*-arylthioureas in the presence of iodine.[562]

The side-chain cyanoethylation of alkyl thienyl ketones with acrylonitrile has been studied[563–565] and used for the preparation of δ-oxonitriles and δ-oxoacids.[564] Aminomethylation (Mannich reaction) of 2-acetylthiophene followed by steam distillation yielded 50% of 2-thienyl vinyl ketone,[566] and has also been used for the synthesis of compounds of biological interest.[567,568]

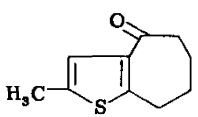
Thienylacetylenes have been prepared in good yield through dehydrohalogenation of 1,2-dichloroethylthiophenes or 1-chlorovinyl thiophenes, which are obtained from acetylthiophenes and PCl_5, with sodium amide and in liquid ammonia.[230,569] The 3-isomers show

[559] E. A. Weilmuenster, R. F. Toomey, W. J. Schubert, W. E. Hill, J. F. Welch, and T. A. Robinson, *J. Org. Chem.* **17**, 404 (1952).
[560] A. J. Hill and R. A. Brooks, *J. Org. Chem.* **23**, 1289 (1958).
[561] I. A. Kaye and I. C. Kogon, *Rec. trav. chim.* **71**, 309 (1952).
[562] G. N. Mahapatra and M. K. Rout, *J. Indian Chem. Soc.* **34**, 653 (1957).
[563] N. A. Acara and R. Levine, *J. Am. Chem. Soc.* **72**, 2864 (1950).
[564] C. W. Yoho and R. Levine, *J. Am. Chem. Soc.* **74**, 5597 (1952).
[565] Yu. K. Yur'ev, G. B. Eliakov, and Z. V. Belyakova, *Vestnik Moskov. Univ., Ser. Mat. Mekh. Astron. Fiz. i Khim.* **11**, 201 (1956); *Chem. Abstr.* **52**, 9067 (1958).
[566] N. I. Putohkin and V. N. Ivanova, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **29**, 3616 (1959).
[567] E. Profft, *Chemiker-Ztg.* **82**, 295 (1958).
[568] W. L. Nobles, *J. Am. Pharm. Assoc. Sci. Ed.* **47**, 895 (1958).
[569] A. Vaitiekunas and F. F. Nord, *J. Org. Chem.* **19**, 902 (1954).

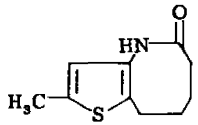
greater stability than the 2-isomers.[230] The direct carbonation of the sodium salts of thienylacetylenes did not lead to α,β-acetylenic acids. The corresponding esters could, however, be obtained with ethyl chlorocarbonate.[570]

The Huang-Minlon modification of the Wolff-Kishner reduction has been used innumerable times for the reduction of thiophenealdehydes and thienyl ketones.[211,219,310,331,343,346,524,526,571] Besides the few references given here, use of this reduction can be found in many papers by Buu-Hoi *et al.*, Goldfarb *et al.*, and Cagniant. The reduction proceeds smoothly with high yields and at lower temperatures than with benzene derivatives. The kinetics of the Wolff-Kishner reduction of diaryl ketone hydrazones has been investigated.[572] The exceptionally low heat of activation for phenyl 2-thienyl ketone agrees with the great ease of reduction of 2-thienyl carbonyl compounds.[572] It was suggested that hydrogen transfer via a cyclic transition state involving the thiophene sulfur was responsible for this.[572] Sterically hindered ketones which do not form hydrazones cannot be reduced through Wolff-Kishner reduction.[387] In these cases, and in those cases when easily reducible halogens are present,[350,387] the Clemmensen reduction is to be preferred. 2-Acetylthiophene has also been reduced in good yield with water gas ($H_2 + CO$) over a cobalt catalyst.[573]

The Beckmann rearrangement of oximes of the thiophene series has been applied (besides the preparation of 2-acetamidothiophene[293]) to thiophenocycloalkenones **(192)** which gave the cyclic amide **(193)** hydrolyzable to the amine **(194)**.[574] The Beckmann rearrangement was

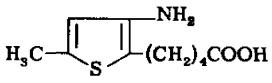


[*192*]



[*193*]

[570] A. J. Osbahr, A. Vaitiekunas, and F. F. Nord, *J. Am. Chem. Soc.* **77**, 1911 (1955).
[571] P. Cagniant and D. Cagniant, *Bull. soc. chim. France* p. 359 (1955).
[572] H. H. Szmant, H. F. Harnsberger, T. J. Butler, and W. P. Barie, *J. Am. Chem. Soc.* **74**, 2724 (1952).
[573] I. Wender, H. Greenfield, and M. Orchin, *J. Am. Chem. Soc.* **73**, 2656 (1951).
[574] B. P. Fabrichnyi, I. F. Shalavina, and Ya. L. Goldfarb, *Zhur. Obshchei Khim.* **31**, 1244 (1961). *Chem. Abstr.* **55**, 23488 (1961).



[194]

also used for the structure determination of the *syn* and *anti* forms of the oxime of 2-chloro-5-acetylthiophene[575] and of thenylidene acetone oxime.[496] The phenylhydrazone of 2-thiophenealdehyde has been rearranged to the *N*-phenylamidine of 2-thenoic acid.[576] Formazyl compounds of the thiophene series were obtained by reacting diazotized anthranilic acid with 2-thiophenealdehyde phenylhydrazone.[577] The reaction of diazonium salts with 3-(2-thienyl)acrylic acid gives 2-styrylthiophenes.[578]

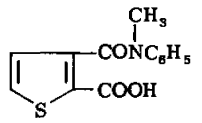
The reaction of alkenylthiophenes with sulfur, or the reaction of ethyl 2-thenoyl acetate with P_2S_5, leads to thienylsubstituted 1,2-dithiole-3-thiones.[579]

Nine esters of 2-thenoic acids have been prepared and the molar refractivities were calculated from refractive indices and densities.[580]

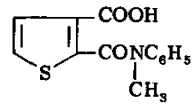
The potassium salt of 2-thiophenecarboxylic acid is rearranged to the potassium salt of 2,5-thiophenedicarboxylic acid and thiophene in the presence of CdO at 400°C.[581] The free 2,5-thiophenedicarboxylic acid is stable up to 320°C.[582]

It has been shown that 2,3-thiophenedicarboxylic acid is preferentially esterified in the 2-position and the dimethyl ester is preferentially hydrolyzed in this position.[583] The structure proof was difficult to achieve as rearrangements occurred. Thus both isomeric amides (**195**) and (**196**) were decarboxylized to the *N*-methylanilide of 3-thiophenecarboxylic acid (**197**).[583] The same carbomethoxy benzoylthiophene, proved to be 2-carbomethoxy-3-benzoylthiophene (**198**),

[575] A. Buzas and J. Teste, *Bull. soc. chim. France* p. 359 (1960).
[576] S. Robev, *Chem. Ber.* **91**, 244 (1958).
[577] M. Seyhan and W. C. Fernelius, *Chem. Ber.* **89**, 2482 (1956).
[578] W. Freund, *J. Chem. Soc.* p. 2889 (1953).
[579] J. Teste and N. Lozach, *Bull. chim. soc. France* p. 492 (1954).
[580] B. Weinstein, *J. Am. Chem. Soc.* **77**, 6709 (1955).
[581] B. Raecke, *Angew. Chem.* **70**, 1 (1958).
[582] H. Hopff and A. Krieger, *Helv. Chim. Acta* p. 1058 (1961).
[583] B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **18**, 138 (1953).



[195]



[196]

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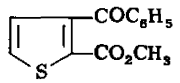
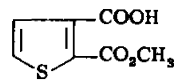
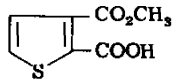


[198]

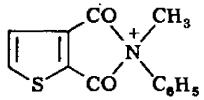


[199]

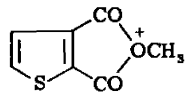


[200]

was obtained through the Friedel-Crafts reaction of the acid chlorides derived from (**199**) and (**200**) with benzene.[583] In addition, rearrangement of (**200**) to (**199**) was observed in the acidic fraction recovered from the Friedel-Crafts synthesis. The rearrangements are supposed to proceed via the cyclic intermediates (**201**) and (**202**).[583]



[201]



[202]

Sodium thenoate is bromodecarboxylated in low yield, slower than sodium anisate, but more rapidly than sodium benzoate.[584] However, the Hunsdiecker reaction with silver salts has been used preparatively for the synthesis of 2,3-dibromo-4-nitrothiophene from 3-bromo-4-nitro-2-thiophenecarboxylic acid.[233]

The Hofmann and Curtius rearrangements have been applied to 2-thienylacryl amides for the preparation of 2-thiophene acetaldehydes.[585] The Hofmann rearrangement proceeds also with 3-thenamides but fails with 2-thenamide.[319]

Cyanothiophenes have been converted to amidines,[586,587] and thienyl-substituted tetrazoles have been prepared from them for pharmacological evaluation.[586]

VII. Reactions Leading to the Destruction of the Thiophene Aromaticity

A. Miscellaneous Reactions

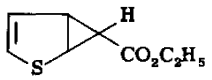
In the earlier sections, the reactions of thiophenes as typical aromatic compounds, always "reverting to type," have been discussed. Now the reactions leading to the destruction of the aromatic system will be treated.

Catalytic reduction of thiophenes over cobalt catalysts leads to thiolane derivatives,[78,588] or hydrocarbons.[588a] Noncatalytic reductions of thiophenes by sodium or lithium in liquid ammonia leads, via the isomeric dihydrothiophenes, to complete destructions of the ring system, ultimately giving butenethiols and olefins.[589-592] Exhaustive chlorination of thiophene in the presence of iodine yields 2,2,3,4,5,5,-hexachloro-3-thiolene.[593] Pyrolysis of thiophene at 850°C gives a

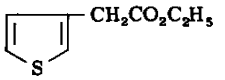
[584] J. D. Berman and C. C. Price, *J. Am. Chem. Soc.* **79**, 5474 (1957).
[585] C. D. Mason and F. F. Nord, *J. Org. Chem.* **16**, 1869 (1951).
[586] B. Elpern, *J. Am. Chem. Soc.* **75**, 661 (1953).
[587] R. Delaby, P. Reynaud, and P. Bercot, *Compt. rend. acad. sci.* **246**, 125 (1958).
[588] H. Greenfield, S. Metlin, M. Orchin, and I. Wender, *J. Org. Chem.* **23**, 1054 (1958).
[588a] P. Truitt, E. H. Holst, and G. Sammons, *J. Org. Chem.* **22**, 1107 (1959).
[589] S. F. Birch and D. T. McAllan, *J. Chem. Soc.* p. 2556 (1951).
[590] S. F. Birch and D. T. McAllan, *J. Chem. Soc.* p. 3411 (1951).
[591] W. Hückel and I. Nabih, *Chem. Ber.* **89**, 2115 (1956).
[592] R. C. Krug and S. Tocker, *J. Org. Chem.* **20**, 1 (1955).
[593] H. L. Coonradt, H. D. Hartough, and H. D. Norris, *J. Am. Chem. Soc.* **74**, 163 (1952).

mixture of the three isomeric bithienyls in 7–8% conversion.[594] Thiophene gives a polymer (mp ≈ 180°C) on treatment with trialkyl aluminum and titanium tetrachloride.[595] From the oxidative degradation of thiophene by nitric acid, maleic acid has been isolated.[596]

Thiophene adds the carbene generated from ethyl diazoacetate to form (**203**) which, on treatment with methanolic hydrogen chloride, is rearranged to ethyl 3-thienylacetate (**204**), whereas the furan analog undergoes ring opening followed by ring closure to a methoxymethyl-α-pyrone.[597] However, treatment of (**203**) with hydrazine and nitrous acid gave (**205**) which with hydrogen bromide was rearranged to thiapyrylium bromide (**206**).[598] The thiapyrylium cation has also



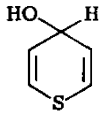
[*203*]



[*204*]

[*205*]

[*206*]



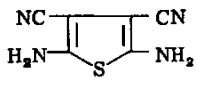
[*207*]

been discovered in the mass spectra of methylthiophenes.[599] The Demjanov rearrangement also leads to the thiopyran system. Thus, treating 2-thenylamine with nitrous acid,[600] or 2-thenyl alcohol with oxalic acid,[601] gave 4-*H*-thiopyran-4-ol (**207**) in low yield.

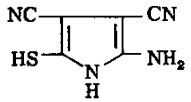
Certain thiophenes can readily be converted to other ring systems. The reversible rearrangement of thiothiophthene (**86**) to a thiophene

[594] H. Wynberg and A. Bantjes, *J. Org. Chem.* **24**, 1421 (1959).
[595] A. V. Topchiev, B. A. Krentse, Yu. A. Goldfarb, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 349 (1959).
[596] L. Lewitt and E. Howard, *J. Am. Chem. Soc.* **76**, 1951 (1954).
[597] G. O. Schenk and R. Steinmetz, *Angew. Chem.* **70**, 504 (1958).
[598] R. Pettit, *Tetrahedron Letters* No. 23, p. 11 (1960).
[599] V. Hanus and V. Cermak, *Collection Czechoslov. Communs.* **24**, 1602 (1959).
[600] N. I. Putokhin and V. S. Egorova, *Doklady Akad. Nauk. S.S.S.R.* **96**, 293 (1954); *Chem. Abstr.* **49**, 5426 (1955).
[601] V. S. Egorova, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **30**, 113 (1960).

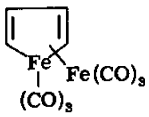
derivative has been mentioned earlier.[175] Another example is the facile rearrangement of 2,5-diamino-3,4-dicyanothiophene (**208**) to 2-amino-3,4-dicyano-5-mercaptopyrrole (**209**).[602] At elevated temper-



[*208*]



[*209*]



[*210*]

atures thiophene and iron carbonyl undergo a novel reaction resulting in the removal of the sulfur atom from the thiophene ring and its substitution by the iron-tricarbonyl group (**210**).[603]

B. Oxidation at the Thiophene Sulfur Atom

The thiophene sulfur atom shows very few of the reactions expected of a sulfide. The oxidation to a sulfone is difficult to achieve, but is of special interest, as knowledge of its aromatic character or lack of it would give information about the ability of sulfur to expand its valence shell beyond eight electrons.

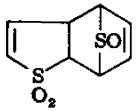
Melles and Backer[604] found, from a study of the oxidation of substituted thiophenes with perbenzoic or peracetic acid, that sulfones could be obtained from polysubstituted methyl- and phenyl-thiophenes and that the presence of electron-attracting groups, such as nitro, hindered the oxidation. Oxidation of thiophene[605,606] led to a product which was formed through a Diels-Alder reaction between the intermediate thiophene sulfoxide (**211**) and thiophene sulfone (**212**) and for which two alternative structures, (**213**) or (**214**), were suggested.[605] Similar "sesquioxides" were also obtained from 2- and 3-methylthiophene and 3-phenylthiophene.[605] The structures were not proved. Bailey and Cummins synthesized thiophene-1,1-dioxide

[602] W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.* **80**, 2822 (1958).
[603] H. D. Kaesz, R. B. King, T. A. Manuel, L. D. Nichols, and F. G. A. Stone, *J. Am. Chem. Soc.* **82**, 4749 (1960).
[604] J. L. Melles and H. J. Backer, *Rec. trav. chim.* **72**, 314 (1953).
[605] J. L. Melles and H. J. Backer, *Rec. trav. chim.* **72**, 491 (1953).
[606] K. Okita and S. Kambara, *Kôgyô Kagaku Zasshi* **59**, 547 (1956); *Chem. Abstr.* **52**, 3762 (1958).

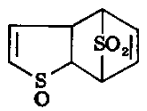
(**212**) in a six-step synthesis from butadiene sulfone utilizing a stepwise exhaustive methylation.[607] Dioxide (**212**) was stable only in dilute solution. In concentrated solution (**212**) dimerizes to (**215**), the structure of which was proved by hydrogenation and independent synthesis of the hydrogenation product.[608] In the Diels-Alder reaction (**212**) reacts as either a diene or dienophile.[609] With 1,2-dimethylenecyclohexane, it reacted as a reactive dienophile yielding (**216**).[609] As a diene it was not very reactive. It did not react with maleic anhy-

[*211*]

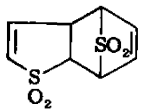
[*212*]



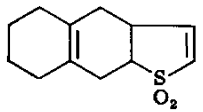
[*213*]



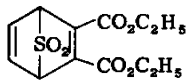
[*214*]



[*215*]



[*216*]



[*217*]

dride, but added acetylene dicarboxylic ester to give (**217**) as well as indene in low yield.[609] 3,4-Dimethylthiophene-1,1-dioxide reacts as

[607] W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.* **76**, 1932 (1954).
[608] W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.* **76**, 1936 (1954).
[609] W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.* **76**, 1940 (1954).

a diene with thionaphthene-1,1-dioxide,[610] and 3,4-diphenylthiophene-1,1-dioxide.[611] 3,4-Dichlorothiophene-1,1-dioxide,[612] obtained by chlorination and dehydrochlorination of butadiene sulfone, reacts both as diene and as dienophile. The thiophene-1,1-dioxides also add bromine.[608,613]

The whole reaction pattern of the thiophene-1,1-dioxides is thus characteristic of unsaturated, and not of aromatic, compounds.

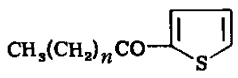
C. Raney Nickel Desulfurization

Through the work of especially Goldfarb *et al.* but also of Buu-Hoi *et al.*, Badger *et al.*, and Wynberg *et al.*, the Raney nickel desulfurization of thiophenes has been developed to an important tool for the synthesis of aliphatic compounds. During the last 5 years over fifty papers have appeared describing applications of this method.

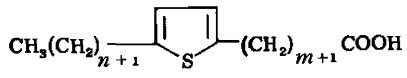
Two different sets of experimental conditions have been used. Buu-Hoi *et al.* and Hansen have employed the method introduced by Papa *et al.*[614] using Raney nickel alloy directly for the desulfurization in an alkaline medium. Under these conditions most functional groups are removed and this method is most convenient for the preparation of aliphatic acids. The other method uses Raney nickel catalysts of different reactivity in various solvents such as aqueous ammonia, alcohol, ether, or acetone. The solvent and activity of the catalyst can have an appreciable influence on yields and types of compounds formed, but have not yet been investigated in detail. In acetic anhydride, for instance, desulfurization of thiophenes does not occur and these reaction conditions have been employed for reductive acetylation of nitrothiophenes.[294] Even under the mildest conditions, all double bonds are hydrogenated and all halogens removed. Nitro and oxime groups are reduced to amines.

Fatty acids are prepared by acylating thiophene with acid chlorides and reducing the ketones (**218**) to alkylthiophenes according to Wolff-Kishner or Clemmensen. The latter are then acetylated and oxidized by hypochlorite to 5-alkyl-2-thiophenecarboxylic acids,[326,615]

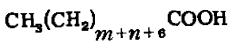
[610] W. Davies and Q. N. Porter, *J. Chem. Soc* p. 459 (1957).
[611] E. W. Duck, *Research Correspondence "Research"* **8**, 47 (1955).
[612] H. Bluestone, R. Bimber, R. Berkey, and Z. Mandel, *J. Org. Chem.* **26**, 346 (1961).
[613] Ya. L. Goldfarb and M. L. Kirmalova, *Doklady Akad. Nauk S.S.S.R.* **91**, 539 (1953); *Chem. Abstr.* **48**, 10723 (1954).
[614] D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.* **14**, 723 (1947).
[615] S. Hansen, *Acta Chem. Scand.* **8**, 695 (1954).



[218]

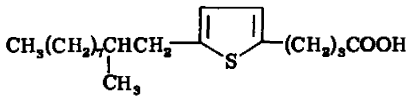


[219]



[220]

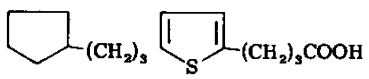
acylated with succinic anhydride or, with the ester chlorides of dicarboxylic acids and the keto acids, reduced to 5-alkyl-2-thienylalkanoic acids (**219**). Desulfurization then yields the desired aliphatic compounds (**220**).[616-622c] The groups can also be introduced in the



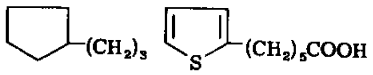
[221]

reverse order.[622] An example is the synthesis of *dl*-tuberculostearic acid from (**221**).[619] In a similar way dihydrohydnocarpic acid and dihydrochaulmoogric acid have been synthesized from (**222**) and (**223**), respectively, by using β-cyclopentylpropionyl chloride, succinic

[616] T. F. Grey, J. F. McGhie, M. K. Pradhan, and W. A. Ross, *Chem. & Ind. (London)* p. 578 (1954).
[617] M. Sy, N. P. Buu-Hoi, and N. D. Xuong, *Compt. rend. acad. sci.* **239**, 1224 (1954).
[618] G. M. Badger, H. J. Rodda, and W. H. E. Sasse, *J. Chem. Soc.* p. 4162 (1954).
[619] M. Sy, N. P. Buu-Hoi, and N. D. Xuong, *Compt. rend. acad. sci.* **239**, 1813 (1954).
[620] N. P. Buu-Hoi, M. Sy, and N. D. Xuong, *Compt. rend. acad. sci.* **240**, 785 (1955).
[621] M. Sy, *Bull. soc. chim. France* p. 1175 (1955).
[622] T. F. Gray, J. F. McGhie, and W. A. Ross, *J. Chem. Soc.* p. 1502 (1960).
[622a] J. F. McGhie, W. A. Ross, D. Evans, and J. E. Tomlin, *J. Chem. Soc.* p. 350 (1962).
[622b] N. Polgar and W. Smith, *Chem. & Ind. (London)* p. 1959 (1961).
[622c] S. Nishimura, S. Otsuka, and E. Imoto, *Nippon Kagaku Zasshi* **82**, 1688 (1961).



[222]

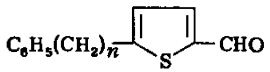


[223]

anhydride, and adipic acid ester chloride as the reagents.[620] ω-Phenyl-substituted alkanoic acids are obtained by using ω-phenylsubstituted fatty acid chlorides in the first acylation step.[621]

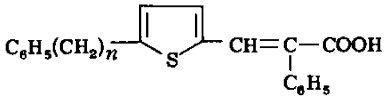
Instead of thiophenes the readily available di-2-thienylmethane can be used as a chain extender, introducing a nine carbon unit upon desulfurization.[623-625] Similarly the two reactive positions of 2,2-bithienyl and 2,2′,5″,2″-terthienyl have been utilized for the introduction of eight and twelve carbons, respectively.[326,328]

Another method of preparing α,ω-diarylated alkanoic acids utilizes the condensation of 5-(ω-phenylalkyl)substituted 2-thiophenealdehydes (**224**) with benzyl cyanides and hydrolysis and desulfurization of the acids obtained (**225**).[626,627] In this way, α,ω-diphenylcaprylic acid has been prepared.[627]



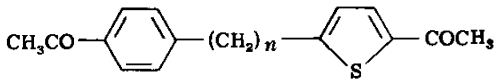
[224]

[623] Ya. L. Goldfarb and M. L. Kirmalova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 509 (1955).
[624] N. P. Buu-Hoi and N. D. Xuong, *Bull. soc. chim. France* p. 1583 (1955).
[625] Ya. L. Goldfarb and M. L. Kirmalova, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. S.S.R.* (*Eng. Transl.*) p. 487 (1957).
[626] N. P. Buu-Hoi and M. Sy, *Compt. rend. acad. sci.* **242**, 2011 (1956).
[627] N. P. Buu-Hoi and M. Sy, *J. Org. Chem.* **23**, 97 (1958).

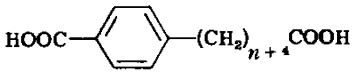


[225]

Dicarboxylic acids have been prepared by the stepwise acylation and Wolff-Kishner reduction of thiophene or di-2-thienylmethane with ester chlorides of dicarboxylic acids.[624] Another method consists of the $AlCl_3$ catalyzed acylation of ω-phenylalkylthiophenes which occurs both in the free thiophenic position and in the *para* position of the ring (**226**). Hypochlorite oxidation and desulfurization then give diacides such as (**227**).[621,628]



[226]



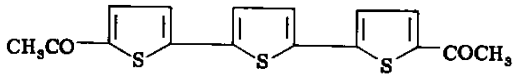
[227]

By the use of Raney nickel alloy in D_2O and NaOD, richly deuterated aliphatic acids have been prepared.[629-630a]

The extent of reduction of the carbonyl group of ketones and keto acids during desulfurization depends on the kind of catalyst used and on the solvent. The W 7 catalyst was most effective in reducing

[628] N. P. Buu-Hoi, M. Sy, and N. D. Xuong, *Compt. rend. acad. sci.* **240**, 442 (1955).
[629] N. P. Buu-Hoi, *Nature* **180**, 385 (1957).
[630] N. P. Buu-Hoi, N. D. Xuong, and N. V. Bac, *Bull. soc. chim. France* p. 1586 (1960).
[630a] N. V. Bac, N. P. Buu-Hoi, and N. D. Xuong, *Bull. soc. chim. France* p. 1077 (1962).

oxo to hydroxy compounds.[622] Lower temperatures favor ketone formation[631] and sterically hindered carbonyls, such as 2-thienyl *t*-butyl ketone, are not reduced.[631] The sensitivity of desulfurization to steric factors is evident by the failure to desulfurize 2,5-di-*t*-butyl-3-acetylthiophene.[631] The carbonyl groups of both aldehydes and ketones can be protected by acetal formation, as particularly cyclic acetals are stable during desulfurization in methanol at room temperature.[631] The free aldehydes give primary alcohols on desulfurization.[632] Another method to obtain only keto compounds is to oxidize the mixtures of ketone and secondary alcohol with CrO_3 after the desulfurization.[326,328] Through the desulfurization of 5,5″-diacetyl-2,2′,5′,2″-terthienyl (**228**), 2,15-hexadecandione (**229**) has been obtained, which



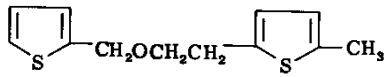
[*228*]

$$CH_3CO(CH_2)_{12}COCH_3$$

[*229*]

has been used in the synthesis of muscone.[328]

From simple ethers of the thiophene series, such as (**230**), aliphatic ethers such as (**231**) have been obtained by desulfurization in ether.[633]



[*230*]

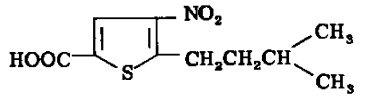
[631] Ya. L. Goldfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 108 (1959).
[632] Ya. L. Goldfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 1013 (1956).
[633] Ya. L. Goldfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 229 (1957).

$$CH_3(CH_2)_4O(CH_2)_6CH_3$$

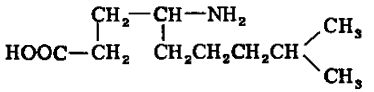
[*231*]

In this way isopentyl pentyl ether, heptyl pentyl ether, and 4,5-bis-methoxymethyl-2,2-dimethylheptane were also prepared from the appropriate thiophene derivatives.[633]

Raney nickel desulfurization has been applied especially to the synthesis of different kinds of amino acids.[633a] α-Amino acids have been prepared by the Strecker synthesis of substituted thiophenealdehydes, followed by desulfurization of the thiophene α-amino acids.[634] α-Amino-*n*-enantic acid, α-amino-*n*-caprylic acid, and norleucin have been obtained in about 50% yield from the appropriate thiophene aldehydes.[634,635] From the desulfurization of thiophene β-amino acids, obtained from the reaction of thiophenealdehydes with malonic acid in ammonia, aliphatic β-amino acids, isolated as acetates, have been obtained in high yields.[636] The desulfurization of 3-nitrothiophenes, such as (**232**), in ammonia leads to γ-substituted amino acids (**233**).[637]



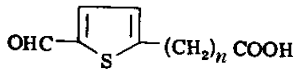
[*232*]



[*233*]

[633a] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *Tetrahedron* **18**, 21 (1962).
[634] Ya. L. Goldfarb and B. P. Fabrichnyi, *Doklady Akad. Nauk SSSR.* **100**, 461 (1955); *Chem. Abstr.* **49**, 8244 (1955).
[635] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **26**, 2893 (1956).
[636] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **28**, 213 (1958).
[637] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **29**, 3596 (1959).

The desulfurization of 2-nitrosubstituted thiophenes proceeds unsatisfactorally.[634] Aminosubstituted aliphatic acids, with the amino group in any desired position, have been obtained through desulfurization of the oximes of the 2-thenoylalkanoic acids obtained on acylation of thiophenes with the ester chlorides of dicarboxylic acids.[638] Better yields are often obtained by reducing the oximes to amines with aluminum amalgam before desulfurization.[638] Another variation is to acylate ethyl ω-2-thienylalkanoates and desulfurize the oximes of the ω-(5-acyl-2-thienyl)alkanoic acids.[639] In this way 9- and 10-aminoundecanoic acid and 11-aminotridecanoic acid have been prepared.[639] Formylation of ethyl ω-(2-thienyl)alkanoates, followed by desulfurization of the oximes of the ω-(5-formyl-2-thienyl)alkanoic acids (**234**), gives ω-aminoalkanoic acids in good yields (**235**).[640] The Strecker synthesis with the aldehydes (**234**) followed by desulfuriza-



[*234*]

$$H_2NCH_2(CH_2)_{n+4}COOH$$

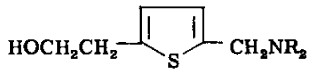
[*235*]

tion has been used for the preparation of aliphatic aminodicarboxylic acids such as 2-aminodecandioic acid and 2-aminoundecanedioic acid.[641]

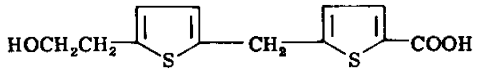
Aliphatic tertiary amines have been prepared by the desulfurization of thenyl-dialkylamines obtained from the Leuckart reaction with 2-

[638] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *Proc. Acad. Sci. USSR. Sect. Chem.* (*Eng. Transl.*) **109**, 371 (1956).
[639] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **29**, 875 (1959).
[640] B. P. Fabrichnyi, I. F. Shalavina, and Ya. L. Goldfarb, *J. Gen. Chem. USSR.* (*Eng. Transl.*) **28**, 2556 (1958).
[641] Ya. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, *Bull. Acad. Sci. USSR., Div. Chem. Sci. SSR.* (*Eng. Transl.*) p. 1311 (1956).

thiophenealdehyde.[642] Aliphatic dialkylamino-alcohols have been prepared by desulfurization of (**236**) obtained by metalation of 2-thenyldialkylamines with butyllithium followed by the reaction with ethylene oxide.[643] In a similar way 12-hydroxyundecanoic acid has been prepared by desulfurization of (**237**).[623] Recently diamines have also been prepared[644] by this method.



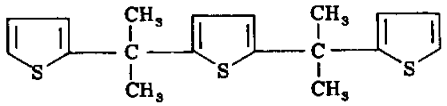
[*236*]



[*237*]

The use of macrocyclic compounds of the thiophene series for the preparation of macrocyclic alicyclic ketones has been mentioned earlier.[348-350] A new synthesis of exaltone has been carried out using (**136**) as the starting material.[350]

Highly branched aliphatic compounds have been obtained by desulfurization of (**98**)[216] and (**238**).[645]



[*238*]

[642] Ya. L. Goldfarb and M. B. Ibragimova, *Proc. Acad. Sci. USSR. Sect. Chem.* (*Eng. Transl.*) **106**, 71 (1956).
[643] Ya. L. Goldfarb and M. B. Ibragimova, *Proc. Acad. Sci. USSR. Sect. Chem.* (*Eng. Transl.*) **113**, 261 (1957).
[644] T. I. Santalova, P. A. Konstantinov, and Ya. L. Goldfarb, *Doklady Akad. Nauk SSSR.* **131**, 1102 (1960); *Chem. Abstr.* **54**, 21103 (1960).
[645] N. P. Buu-Hoi, M. Sy, and N. D. Xuong, *Rec. trav. chim.* **75**, 463 (1956).

In the desulfurization of 3-substituted thiophenes several stereoisomers may be formed in certain cases. Both meso and racemic compounds have been obtained from the desulfurization of 3,4-diaryl-substituted thiophenes.[646] It is claimed, however, that only meso β,β-diphenyladipic acid is obtained upon desulfurization of 3,4-diphenyl-2,5-thiophenedicarboxylic acid[645] and only *dl*-isoleucin from 3-thienylglycine.[233] The formation of small amounts of dimeric products in the desulfurization has been discussed with reference to the mechanism of this reaction.[647]

Raney cobalt is generally less effective than Raney nickel,[648] but may be of use when the rupture of other bonds must be avoided.[644]

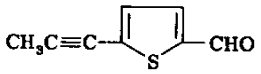
The important use of Raney nickel desulfurization for the structure determination of thiophenes and for the determination of the absolute configuration of optically active thiophene and benzene derivatives has been stressed earlier.

VIII. Biologically Important Thiophenes

A. Naturally Occurring Thiophenes

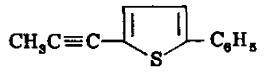
The recent discoveries of thiophene compounds in fungi and higher plants has awakened the interest of the natural product chemist in the chemistry of thiophenes. In 1947 Zechmeister and Sease[649] isolated terthienyl from a special variety of African marigold, *Tagetes erecta*. The search for thiophene compounds in nature increased rapidly when Birkinshaw and Chaplen[650] in 1955 found that the odoriferous constituent of the basidiomycete, *Daedelia juniperina*, which they called junipal, was 5-(1-propynyl)-2-thiophenealdehyde (**239**). The total syntheses of junipal have recently been described.[651,652] The intermediate in these syntheses, 2-(1-propynyl)thiophene, was prepared by alkylation of sodium 2-thiopheneacetylide[651] or through bromination and dehydrobromination of 2-(1-propenyl) thiophene[652] prepared from thiophene and propionic aldehyde. Vilsmeier formylation[652] or the reaction with *n*-butyllithium and *N,N*-dimethyl formamide[651] would then give junipal.

[646] O. Dann and G. Hauck, *Arch. Pharm.* **293**, 187 (1960).
[647] G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.* p. 3862 (1957).
[648] G. M. Badger, N. Kovanko, and W. H. F. Sasse, *J Chem. Soc.* p. 440 (1959).
[649] L. Zechmeister and J. W. Sease, *J. Am. Chem. Soc.* **69**, 273 (1947).
[650] J. H. Birkinshaw and P. Chaplen, *Biochem. J.* **60**, 255 (1955).
[651] L. Skatteböl, *Acta Chem. Scand.* **13**, 1460 (1959).
[652] K. E. Schulte and N. Jantos, *Arch. Pharm.* **292**, 536 (1959).



[239]

The discovery of junipal focused the attention of Sörensen, who had been investigating the occurrence of polyacetylenes in Compositae, on the possibility that these acetylenes were accompanied by thiophenes.[653] From *Coreopsis grandiflora* Hogg ex sweet, 2-phenyl 5-(1-propynyl)thiophene (**240**) was isolated and its structure confirmed by synthesis of the tetrahydro compound, 2-phenyl-5-*n*-propylthiophene.[653] From the root of tansy, the *cis* and *trans* isomers of methyl 5-(1-propynyl)-2-thienylacrylate (**241**) have been isolated.[654] The total synthesis of *trans* (**241**) was achieved by reacting junipal with methylcarbethoxy triphenylphosphonium bromide (Wittig reaction).[651] Several monosubstituted thiophenes, (**242**), (**243**), and



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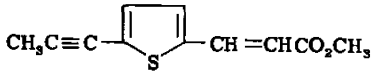

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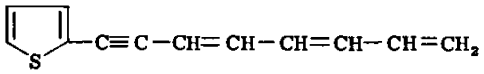

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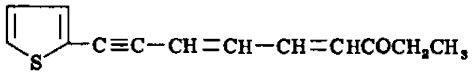
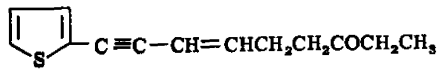


[243]

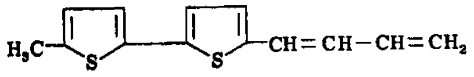
[653] J. S. Sörensen and N. A. Sörensen, *Acta Chem. Scand.* **12**, 771 (1958).
[654] E. Guddal and N. A. Sörensen, *Acta Chem. Scand.* **13**, 1185 (1959).



[244]

(244), have been isolated from scentless mayweed.[655] The synthesis of (242) and (243) have been achieved from 2-thienylacetylene by the Jutz synthesis.[655]

From *Bidens* species, 5-methyl 5′-butadienyl-2,2′-bithienyl (245) has been isolated, the constitution of which was confirmed synthetically.[655] Another 2,2′-bithienyl derivative has been isolated as an additional nematodicidal principal of the roots of *Tagetes*, for which structure (246) has been suggested.[656] On the other hand Sörensen *et al.* have isolated from the thistles, *Berkheya macrocephala* and *Echinops spareocephalus*, a compound with very similar UV and IR spectra as (246) for which they suggested structure (247), based on



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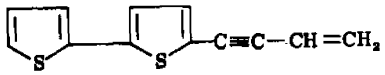
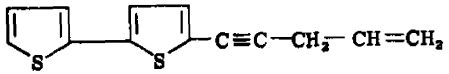


[246]



[247]

[655] N. A. Sörensen, *Pure and Appl. Chem.* **2**, 569 (1961).
[656] J. H. Uhlenbroek and J. D. Bijloo, *Rec. trav. chim.* **78**, 382 (1959).

comparison of its UV spectrum with those of (245) and of monoethylene and monoacetylene derivatives of 2,2′-bithienyl.[655]

It seems quite obvious that the thiophenes are related to the polyacetylenes which they accompany. This viewpoint has recently been illustrated by the formation of thiophenes from polyacetylenes and hydrogen sulfide under almost "biological conditions." In a recent lecture summary, the preparation of terthienyl, junipal, and (241) from 1,4-disubstituted butadiynes and hydrogen sulfide is claimed.[657] A large number of bithienyls have been prepared and their nematodicidal activity investigated. All the compounds with strong activity were found to be derivatives of 2,2′-bithienyl.[658]

Thiophene and methylthiophenes have been found in virgin petroleum.[659] 3,4,5-Trimethyl-2-methylthiothiophene has been isolated from a concentrate of sulfur compounds obtained in the refining of Middle East kerosene.[660]

B. Compounds of Pharmacological Interest

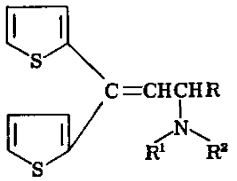
During recent years a certain slackening in interest in the preparation of thiophenes for pharmacological studies can be noticed. As an excellent review on the biological activity of thiophenes has recently been published,[5] the latest developments in this field will only briefly be sketched.

The study of the β-thienylalanines and of peptides derived from them as antimetabolites has been continued.[129,661-663]

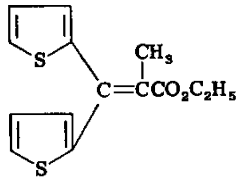
The potent analgesics derived from 3-tertiary amino-1,1-di-(2-thienyl)-1-butene (248) (thiambutenes) have been studied especially by Japanese workers.[664-667] It has been shown that it is the enantio-

[657] L. Hörner, *Angew. Chem.* **74**, 42 (1962).
[658] J. H. Uhlenbroek and J. D. Bijloo, *Rec. trav. chim.* **79**, 1181 (1960).
[659] C. J. Thompson, H. J. Coleman, L. Mikkelsen, D. Yee, C. C. Waid, and H. T. Rall, *Anal. Chem.* **28**, 1384 (1956).
[660] S. F Birch, T. V. Cullum, R. A. Dean, and D. G. Redford, *Tetrahedron* **7**, 311 (1959).
[661] F. W. Dunn, *J. Biol. Chem.* **227**, 575 (1957).
[662] F. W. Dunn, *J. Biol. Chem.* **233**, 411 (1958).
[663] N. Kaufman, J. V. Klavins, and T. D. Kinney, *J. Nutrition* **75**, 93 (1961).
[664] T. Kametani and Y. Akazawa, *Yakugaku Zasshi* **73**, 649 (1953); *Chem. Abstr.* **48**, 5175 (1954).
[665] N. Sugimoto and S. Saito, *Yakugaku Zasshi* **73**, 757 (1953); *Chem. Abstr.* **48**, 9367 (1954).
[666] I. Hirao, K. Mizunuma, and M. Hayashi, *Yakugaku Zasshi* **74**, 105 (1954); *Chem. Abstr.* **49**, 1696 (1955).
[667] T. Yabuuchi, *Chem. & Pharm. Bull. (Tokyo)* **8**, 1041 (1960).

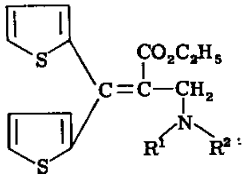
morph related to D-alanine which is the analgesically active optical isomer.[668] Methods for the detection of the thiambutenes have been described.[669] The Reformatsky reaction between di-2-thienyl ketone and ethyl α-bromopropionate followed by dehydration, gave (**249**).



[*248*]



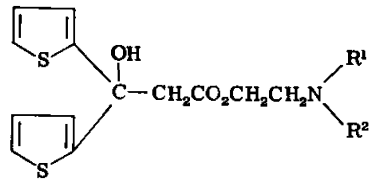
[*249*]



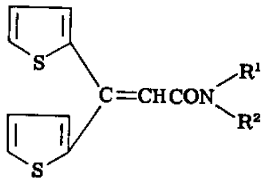
[*250*]

Bromination of the methyl group of (**249**) with *N*-bromosuccinimide, followed by reaction with excess secondary amine gave (**250**) which shows combined analgesic and antitussive properties.[670] The Reformatsky reaction has also been used for the preparation of 2-aminoethyl 3,3-diaryl-3-hydroxypropanates (**251**) as well as their dehydration products.[671] The propene amides (**252**) have also been prepared for pharmacological evaluation.[672] In 1-methyl-3-bis(2-thienyl)-

[668] A. H. Beckett and A. F. Casy, *J. Chem. Soc.* p. 900 (1955).
[669] S. Akiya, Y. Nakazawa, and S. Ishikura, *Yakugaku Zasshi* **77**, 931 (1957).
[670] N. Shigematsu and G. Hayashi, *Yakugaku Zasshi* **81**, 421 (1961); *Chem. Abstr.* **55**, 17618 (1961).
[671] R. Kimura, T. Yabuuchi, and Y. Tamura, *Chem. & Pharm. Bull. (Tokyo)* **8**, 103 (1960). *Chem. Abstr.* **55**, 5454 (1961).
[672] T. Yabuuchi, *Chem. & Pharm. Bull. (Tokyo)* **8**, 169 (1960); *Chem. Abstr.* **55**, 5454 (1961).



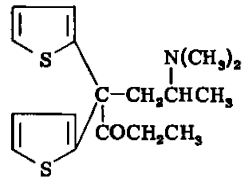
[*251*]



[*252*]

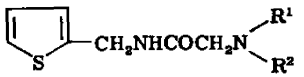
methylenepiperidine, a potent nonnarcotic antitussive has been found.[673] It is claimed to be more potent than codeine and shows no analgesic activity. 3-Piperidino-1,1-bis(2-thienyl)butene has been tested clinically as an antitussive.[674]

The thiophene analog of methadone (**253**) and isomethadone have been prepared and shown to be active analgesics.[675] Heterocyclic acetamides of the type (**254**) have been prepared for evaluation of their analgesic and antipyretic activity.[676,677]



[*253*]

[673] Y. Kase, T. Yuizone, T. Yamasaki, T. Yamada, S. I. M. Tamiya, and I. Kondo, *Chem. & Pharm. Bull. (Tokyo)* **7**, 372 (1959); *Chem. Abstr.* **54**, 22625 (1960).
[674] R. Kimura, M. Ogawa, and T. Yabuuchi, *Chem. & Pharm. Bull. (Tokyo)* **7**, 171 (1959); *Chem. Abstr.* **54**, 22625 (1960).
[675] E. A. Schildknecht and E. V. Brown, *J. Am. Chem. Soc.* **77**, 954 (1955).
[676] E. Szarvasi and L. Neuvy, *Compt. rend. acad. sci.* **252**, 1163 (1961).
[677] E. Szarvasi and L. Neuvy, *Bull. soc. chim. France* p. 944 (1961).



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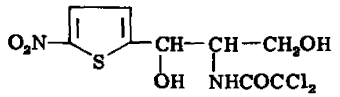
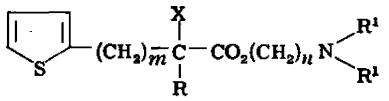


[255]

The thiophene analog of chloramphenicol (**255**) has been synthesized,[529,678-680] as also have been similar structures. The antibacterial activity of all was much lower than that of the natural antibiotic.[681]

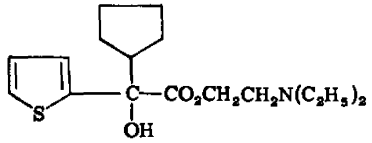
The thioamide of 2-thenoic acid has been prepared in a study of potential antitubercular compounds.[682] It did not surpass thioisonicotinamide in antitubercular activity. The thiosemicarbazones of thiophenealdehydes and ketones (cf. Section VII,D) show high activity against *Mycobacterium tuberculosis*, but are very toxic. The thiosemicarbazone of 4-(2-thienyl)-3-buten-2-one has been reported to be capable of completely inhibiting the *in vitro* growth of *M. tuberculosis* even in relatively low concentrations.[491]

Earlier investigations have shown that powerful antispasmodic activity occurs in various basic esters of α-substituted thienylglycolic acids, thienylacetic acids, and thienylpropionic acids of the general type (**256**), (cf. reference 5 for details). One such compound, the



[256]

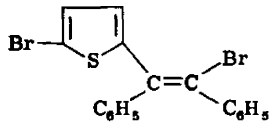
[678] O. Dann, H. Ullrich, and E. F. Moller, *Z. Naturforsch.* **7**, 344 (1952).
[679] E. C. Herman and A. Kreuchunas, *J. Am. Chem. Soc.* **74**, 5168 (1952).
[680] C. F. Huebner, P. A. Diassi, and C. R. Schulz, *J. Org. Chem.* **18**, 21 (1953).
[681] M. C. Rebstock and C. D. Stratton, *J. Am. Chem. Soc.* **77**, 3082 (1955).
[682] R. I. Meltzer, A. D. Lewis, and J. A. King, *J. Am. Chem. Soc.* **77**, 4062 (1955).



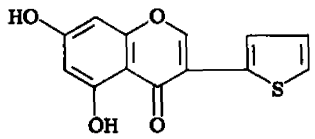
[257]

2-diethylaminoethyl ester of α-cyclopentyl-(2-thienyl)glycolic acid (**257**), is employed clinically in the form of its salt. The most recent work is concerned with the basic alkyl esters of α-(2-cycloalkenyl)-2-thienylacetic acids, which have been pharmacologically evaluated in the form of their acid addition and quaternary ammonium salts.[683,684] Several have been found to possess anticholinergic activity of a high order.

Many stilbenelike thiophene compounds have been prepared for a study of estrogenic activity, especially by Buu-Hoi *et al.* Thiophene derivatives of nonhydroxylated stilbene types showed no significant activity,[478,525,685] whereas weak estrogenic activity was found in 5-acetyl-, 5-propionyl-, and 5-benzoyl-2-(-stilbenyl)thiophene.[686] 1-Bromo-1,2-diphenyl-2-(5-bromo-2-thienyl)ethylene (**258**) was found to inhibit body growth and to produce extensive testicular atropy in male rats.[687] A thiophene analog of estrogenic isoflavones (**259**)



[258]



[259]

showed no activity.[438]

[683] F. Leonard and L. Simet, *J. Am. Chem. Soc.* **77**, 2855 (1955).
[684] F. H. McMillan and C. C. Scott, *J. Am. Pharm. Assoc., Sci. Ed.* **45**, 578 (1956).
[685] N. P. Buu-Hoi and N. Hoan, *J. Org. Chem.* **17**, 350 (1952).
[686] P. Gley, N. P. Buu-Hoi, N. H. Nam, N. D. Xuong, and J. Delor, *Bull. soc. chim. biol.* **36**, 1249 (1954).
[687] N. P. Buu-Hoi, *Acta Univ. Intern. contra Cancrum* **13**, 442 (1957).

β-Chloroethylamino derivatives of thiophene were found to be quite toxic and inhibited the growth of tumors (sarcoma "45," Ehrlich's tumor) only slightly.[688]

2-Thiopheneglyoxal has been found to be only moderately active against Newcastle disease virus and influenza virus in embryonated eggs.[689]

The antiadrenaline and antinoradrenaline activity of *N*-benzyl-*N*-2′-halogenoethyl 2-thenylamines has been studied,[690] as has the radiation protective action of *N*-phenylamidines of thiophenecarboxylic acid in white rats.[691]

[688] Ya. L. Goldfarb and M. S. Kondakova, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)* **30**, 107 (1960).
[689] R. B. Moffett, B. D. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *J. Am. Chem. Soc.* **79**, 1687 (1957).
[690] N. B. Chapman and A. J. Tompsett, *J. Chem. Soc.* p. 1291 (1961).
[691] I. Baev and S. Robev, *Compt. rend. acad. bulgare sci.* **13**, 733 (1960).

Reactions of Acetylenecarboxylic Acids and Their Esters with Nitrogen-Containing Heterocyclic Compounds

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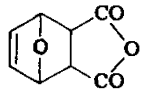
I. Historical Introduction

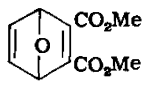
Soon after the discovery of the addition reaction between dienophiles and dienes which now bears their names, Diels and Alder extended their investigations to include potential heterocyclic dienes. In 1929 the first compound investigated, furan,[1] was observed to combine with maleic anhydride, like butadiene in a typical Diels-Alder reaction, across the 2,5-positions yielding a 1:1 molar adduct

[1] O. Diels, K. Alder, and E. Naujoks, *Ber. deut. chem. Ges.* **62**, 554 (1929).

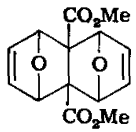
(1). Dimethyl acetylenedicarboxylate gave[2] first a similar adduct (2) which then added further molecules of furan yielding (3) and subsequently (4). Between 1931 and 1940 the reactions of acetylenedicarboxylic acid and its dimethyl ester with a number of nitrogen containing heterocyclic compounds were examined, and structures were proposed for the products. Apart from an unpublished investigation[3] of the products from pyridine and dimethyl acetylenedicar-



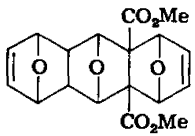
[1]



[2]



[3]



[4]

boxylate in 1945, interest in this subject lapsed until 1954 when the structures originally proposed[4] for the adducts from this ester, acridine and methanol, were revised.[5] Subsequent investigations involving the use of modern physical methods which were not available in the 1931–1940 period have shown that a number, but by no means all, of the structures originally assigned to adducts from dimethyl acetylenedicarboxylate and nitrogen-containing heterocyclic compounds required revision.

II. Main Types of Reaction Now Recognized

Both acetylenedicarboxylic acid and its ester undergo Michael addition reactions with a variety of nucleophilic reagents. An example[6] is

[2] O. Diels, K. Alder, N. Nienborg, and O. Schmalbeck, *Ann. Chem. Liebigs* **490**, 243 (1931); O. Diels and S. Olsen, *J. prakt. Chem.* **156**, 285 (1940).

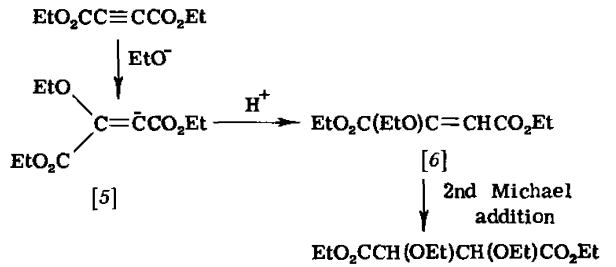
[3] R. B. Woodward, personal communication; E. C. Kornfeld, Ph.D. thesis, Harvard 1945.

[4] O. Diels and W. E. Thiele, *Ann. Chem. Liebigs* **543**, 79 (1939).

[5] R. M. Acheson and M. L. Burstall, *J. Chem. Soc.* p. 3240 (1954).

[6] A. Michael and J. E. Bucher, *Ber. deut. chem. Ges.* **29**, 1792 (1896).

the reaction of sodium ethoxide with the ethyl ester when a mixture of diethyl ethoxy-fumarate and -maleate (6) is obtained along with diethyl diethoxysuccinate (7), which is formed by a subsequent addition. Reaction presumably proceeds through the attack of the



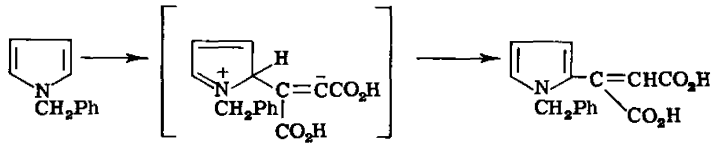
[5] [6] [7]

ethoxide ion on the triple bond under the activation of the carbonyl group leading to the intermediate anion (5), which subsequently takes up a proton. If the general assumption is made that this type of anion is the first intermediate in the reaction of acetylenedicarboxylic acid or its esters with nitrogen-containing heterocyclic compounds, then the formation of all the known products with recognized structures can be accounted for.

A. Simple Michael-Type Additions

1. *With Protons Provided by the Acetylene or Heterocyclic Reactant*

Pyrroles react at free α- or β-positions with acetylenedicarboxylic acid or the methyl ester yielding mixtures of the corresponding maleic and fumaric acid derivatives.[7] Protons are readily available to satisfy



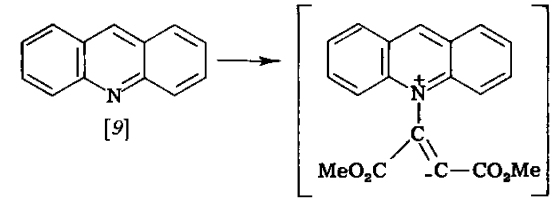
[8]

[7] L. Mandell and W. E. Blanchard, *J. Am. Chem. Soc.* **79**, 6198 (1957).

the demand of the carbanion (**8**) in this instance and in the case of the acetylenic ester and *N*-unsubstituted pyrroles, but other reactions can also occur (see following).

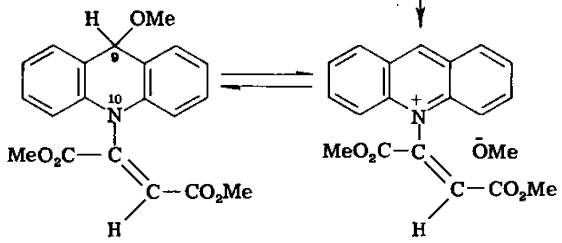
2. *With Protons Provided by the Solvent*

Acridine (**9**) combines readily with dimethyl acetylenedicarboxylate in methanol[5] yielding the methoxide (**11**), which is in equilibrium with the corresponding 9-methoxy-9,10-dihydroacridine (**12**). Presumably the first formed zwitterion (**10**) abstracts a proton from the solvent,



[*9*]

[*10*]



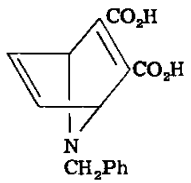
[*12*] [*11*]

since no other source is available.

B. Diels-Alder Additions to Pyrroles

A small number of pyrroles undergo addition of acetylenedicarboxylic acid across the 2,5-positions yielding adducts similar to those obtained from cyclopentadiene. In the case of 1-benzylpyrrole and the acid, some (**13**) is formed,[7] probably through the intermediary of a species such as (**8**); a strong case has been made[8] for the supposition that the Diels-Alder reaction occurs in two distinct stages.

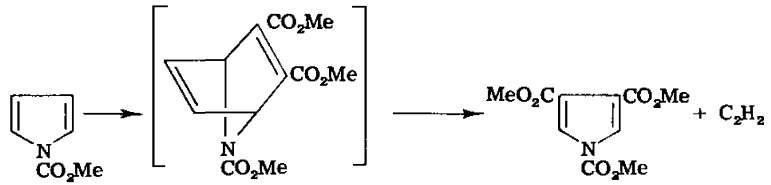
[8] R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959).



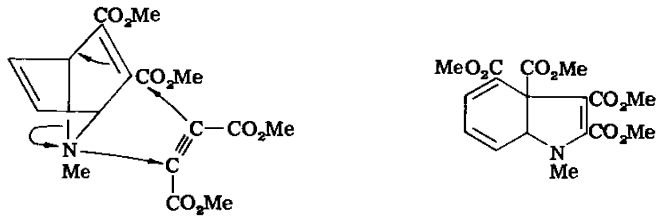
[*13*]

C. Further Reactions of the Diels-Alder Type Adducts

Methyl pyrrole-1-carboxylate (**14**) and hot dimethyl acetylenedicarboxylate give trimethyl pyrrole-1,3,4-tricarboxylate (**15**) and acetylene, presumably through the addition–elimination sequence shown.[9] Dimethyl acetylenedicarboxylate and 1-methylpyrrole combine yielding the dihydroindole (**17**). This is readily explained by assuming that the adduct (**16**) is first formed and then combines with a second molecule of the ester as indicated.[10]



[*14*] [*15*]



[*16*] [*17*]

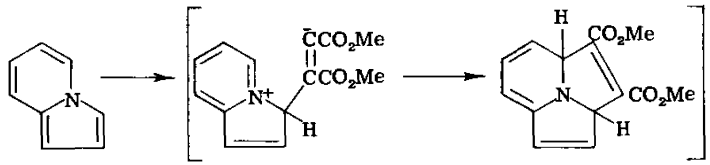
[9] R. M. Acheson and J. M. Vernon, *J. Chem. Soc.* p. 457 (1961).

[10] R. M. Acheson, A. R. Hands, and J. M. Vernon, *Proc. Chem. Soc.* p. 164 (1961); R. M. Acheson and J. M. Vernon, *J. Chem. Soc.* p. 1148 (1962).

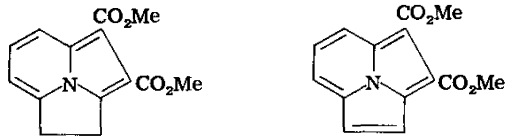
D. Further Reactions of the Initial Michael-Type Zwitterions

1. *Direct Cyclization*

Indolizine (**18**) combines[11,12] with dimethyl acetylenedicarboxylate in the presence of palladium on charcoal yielding two products, (**19**) and (**20**), which may be formed as indicated.



[*18*]



[*19*]

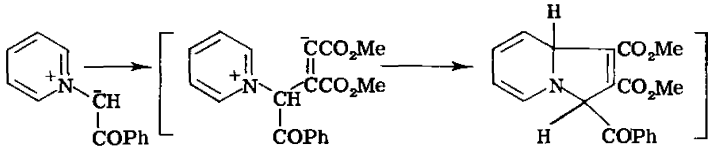
[*20*]

The zwitterion (**22**) obtained from 1-phenacylpyridinium bromide (**21**) and dimethyl acetylenedicarboxylate in the presence of palladium on charcoal yields[13] the indolizine (**23**) possibly through the route shown.

2. *Addition of a Second Mole of Dimethyl Acetylenedicarboxylate to the Initial Zwitterion*

a. Many pyridines[14] react with dimethyl acetylenedicarboxylate under aprotic conditions yielding 1:2 molar adducts (**26**), some of

[11] A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.* **24**, 582 (1959).
[12] A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.* **83**, 453 (1961).
[13] V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.* **83**, 458 (1961).
[14] R. M. Acheson and G. A. Taylor, *Proc. Chem. Soc.* p. 186 (1959); *J. Chem. Soc.* p. 1691 (1960).

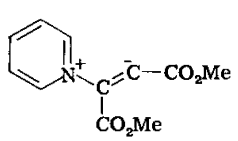


[*22*]

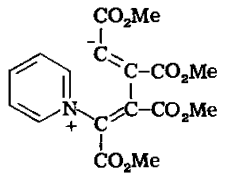
[*21*]

[*23*]

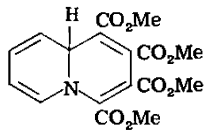
which rapidly isomerize to structures such as (**27**). The first formed zwitterion (**24**) probably reacts with a second molecule of the ester giving (**25**) and cyclization follows.



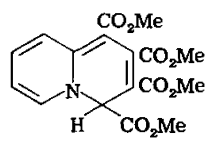
[*24*]



[*25*]



[*26*]

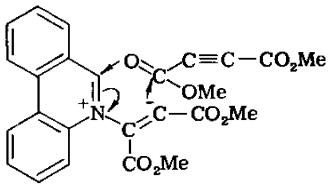


[*27*]

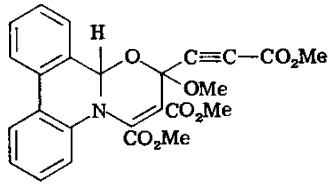
b. In one instance, so far, an alternative reaction has been detected.[15] A minor product in the case of phenanthridine is (**29**) which can be accounted for by assuming that the initially formed zwitterion

[15] R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, p. 3758 (1962).

(28) reacts in an alternative mode with a second molecule of the ester.



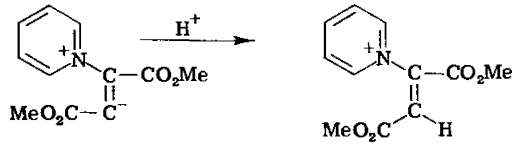
[28]



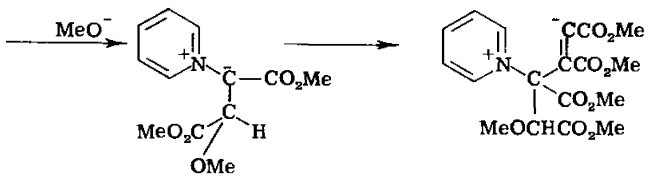
[29]

3. *Addition of a Mole of Methanol and a Second Mole of Dimethyl Acetylenedicarboxylate to the Initial Zwitterion*

Pyridine and dimethyl acetylenedicarboxylate in methanol yield[16,17] a mixture of (33) and (34). It is tempting to assume that a zwitterion (30) is first formed and that this then adds a proton followed by a methoxide ion (Michael addition) under the influence of both the positive charge on the ring and the assisting ester group. The resulting structure (31) could then add another molecule of the ester and cyclize, as indicated, to (32). Subsequent aromatization accompanied by loss of one, or the other, substituent at position 3 would lead to the two products, (33) and (34), actually isolated.

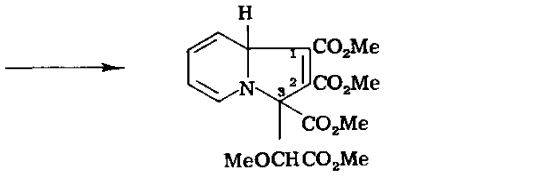


[30]

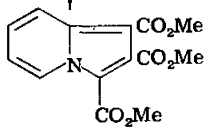


[31]

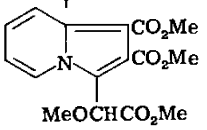
[16] O. Diels, and R. Meyer, *Ann. Chem. Liebigs* **513**, 129 (1934).
[17] A. Crabtree, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.* p. 3497 (1961).



[32]



[33]



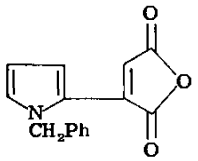
[34]

III. Reactions of Acetylenic Acids and Esters with Individual Nitrogen-Containing Heterocyclic Compounds

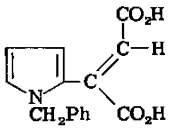
A. Pyrroles

1. *With Acetylenic Acids*

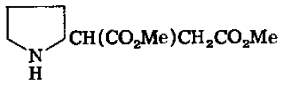
Acetylenedicarboxylic acid is known to combine with a number of pyrroles but only in the case of 1-benzylpyrrole have the products been rigorously examined. Mandell and Blanchard[7] showed that in this case a mixture of the maleic anhydride (35), the fumaric acid (36), and the Diels-Alder type adduct (38) was formed.



[35]



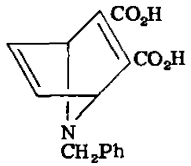
[36]



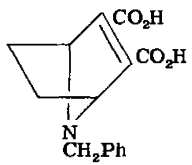
[37]

The anhydride (35) with water gave an acid isomeric with (36), and complete hydrogenation of both acids followed by esterification gave the same compound (37). Four moles of hydrogen were absorbed and the benzyl group was split off. Only three moles of hydrogen

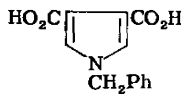
were absorbed in a corresponding reduction of the third adduct (38) and hydrogenation under other conditions gave (39). This last, on heating with aqueous sodium carbonate, gave 1-benzylpyrrole-3,4-dicarboxylic acid (40) which decarboxylated to 1-benzylpyrrole with



[38]



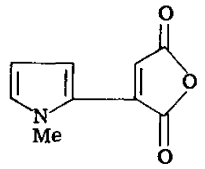
[39]



[40]

hot dilute hydrochloric acid. The third adduct (38) with aqueous sodium carbonate also broke down to 1-benzylpyrrole and, after working up, to the anhydride (35).

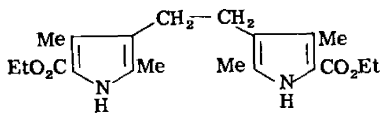
Diels *et al.*[18] showed that acetylenedicarboxylic acid and 1-methylpyrrole gave 1-methyl-2-pyrrylmaleic anhydride (41) and a second compound. The anhydride on hydrogenation and conversion to the corresponding dimethyl ester gave the same product as obtained from 1-methylpyrrole and maleic anhydride, followed by hydrolysis and



[41]

esterification. The second compound, described as the maleic acid corresponding to (41), is probably the fumaric acid, but a structure analogous to (38) is not excluded. Ethyl 3,5-dimethylpyrrole-2-carboxylate and acetylenedicarboxylic acid gave[19] a good yield of a 1:1 molar adduct which has not been further investigated, whereas ethyl 3,5-dimethylpyrrole-2-carboxylate and propiolic acid are stated[20] to yield (42).

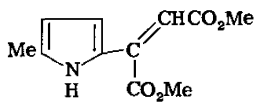
[18] O. Diels, K. Alder, and H. Winckler, *Ann. Chem. Liebigs* **490**, 267 (1931).
[19] H. Fischer, P. Hartmann, and H-J. Riedl, *Ann. Chem. Liebigs* **494**, 246 (1932).
[20] H. Fischer and H. Gademann, *Ann. Chem. Liebigs* **550**, 196 (1942).



[42]

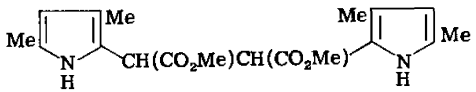
2. *With Acetylenic Esters*

Dimethyl acetylenedicarboxylate with 2-methylpyrrole gives[21] two 1:1 molar adducts, both of which on hydrogenation absorbed one mole of hydrogen and gave the same product. The original adducts are, therefore, the dimethyl 2-methyl-5-pyrryl-fumarate (43) and -maleate, but which is which was not established. An exactly similar situation[21] refers to 2,3-dimethylpyrrole, and only one adduct was

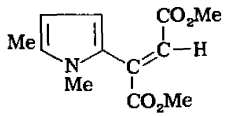


[43]

obtained from 2,3,4-trimethylpyrrole. 2,4-Dimethylpyrrole and dimethyl acetylenedicarboxylate gave[18] a product analyzing for the bis-Michael adduct (44), whereas 1,2-dimethylpyrrole and the ester gave[22] (45).



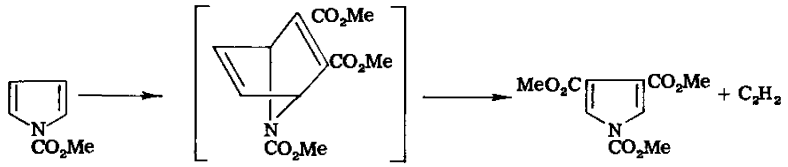
[44]



[45]

[21] O. Diels, K. Alder, H. Winckler, and E. Petersen, *Ann. Chem. Liebigs* **498**, 1 (1932).
[22] R. M. Acheson, A. O. Plunkett, and J. M. Vernon, unpublished data.

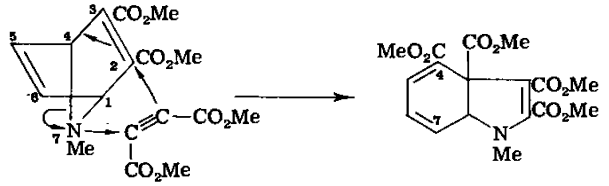
Methyl pyrrole-1-carboxylate and dimethyl acetylenedicarboxylate combine at 170°–200°C, giving trimethyl pyrrole-1,3,4-tricarboxylate (**46**) and acetylene.[9] This reaction probably proceeds through the



[46]

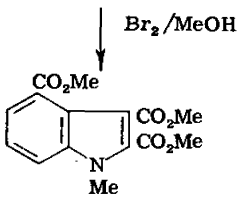
Diels-Alder type intermediate as indicated, and there is an analogy in the decomposition of (**39**) with alkali to (**40**).

1-Methylpyrrole and dimethyl acetylenedicarboxylate interact at 0°C to give a 1:2 adduct which is now known[10] to have structure (**48**). It is formed by addition of the ester across the 2,5-positions of the pyrrole yielding (**47**), which was not isolated but combined with a second molecule of the ester across the 2,7-positions accompanied by scission of the 4,7-bond as indicated. This adduct (**48**) was oxidized by bromine in methanol to trimethyl 1-methylindole-2,3,4-tricarboxylate and reacted further with hot dimethyl acetylenedicarboxylate.



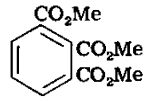
[47]

[48]

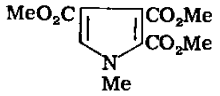


The products were trimethyl hemimellitate (**49**) and trimethyl 1-methylpyrrole-2,3,4-tricarboxylate (**50**), which were presumably

formed by the acetylene adding across the 4,7-positions of the dihydroindole (**48**) followed by the breakup of the resulting structure to the two aromatic products isolated.

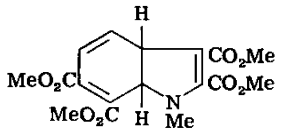


[49]

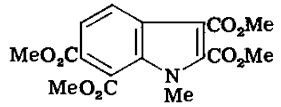


[50]

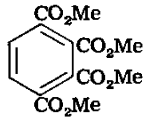
When the original reaction between the 1-methylpyrrole and dimethyl acetylenedicarboxylate was carried out on a larger scale with inadequate cooling, an exothermic reaction took place and none of the dihydroindole (**48**) could be detected among the products.[10] However these included the mellitic ester (**49**) and the pyrrole (**50**), indicating that some of the dihydroindole (**48**) had formed and had combined with more of the acetylenic ester as already described. A decomposition product of the dihydroindole as yet unidentified, tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate (**52**), and tetramethyl prehnit-



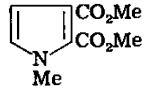
[51]



[52]



[53]



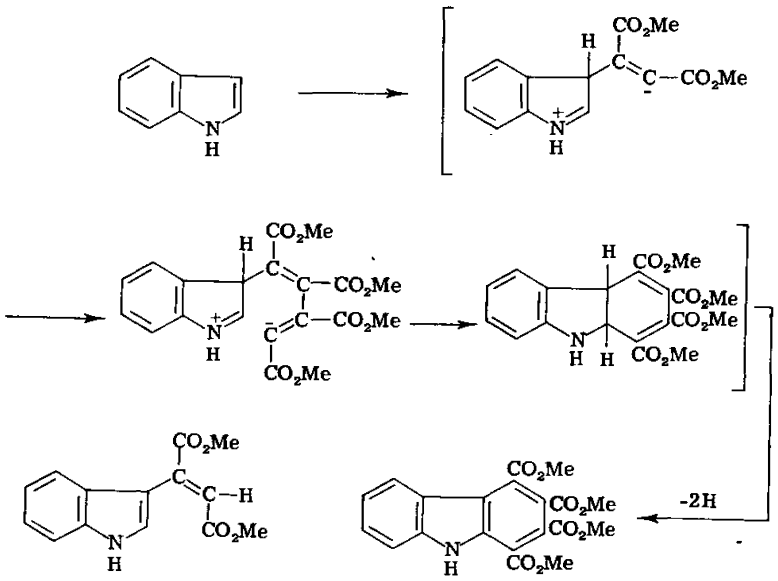
[54]

ate (**53**) were also isolated. The formation of the indole tetraester (**52**) is readily accounted for, as the dimethyl acetylenedicarboxylate can add to the initial 1:1 molar adduct (**47**) in the alternative sense to that leading to the dihydroindole (**48**), i.e., across the 6,7-positions with the breaking of the 4,7-bond. The resulting dihydroindole (**51**) by loss of hydrogen would yield the indole tetraester (**52**) isolated and an alternative reaction of (**51**) with dimethyl acetylenedicar-

boxylate accounts for the tetramethyl prehinitate; the pyrrole (**54**) expected as the other product from this last reaction was not detected in the unresolved reaction product.

B. Indoles

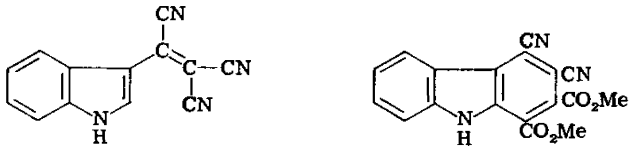
Indole on standing with dimethyl acetylenedicarboxylate for 74 days gave a 63% yield of the carbazole (**55**) along with 7–8% of each of two 1:3 molar adducts and about 2% of a 2:1 molar adduct for which no structures were suggested. It was proposed[23] that the fumarate (**56**) was an intermediate, as it gave the carbazole (**55**) with the ester. However, as the yield in this last reaction, 26%, is much less than that obtained in the direct addition, it is very unlikely that (**56**) is, in fact, an intermediate, and an alternative reaction scheme as suggested here may be applicable.



[56] [55]

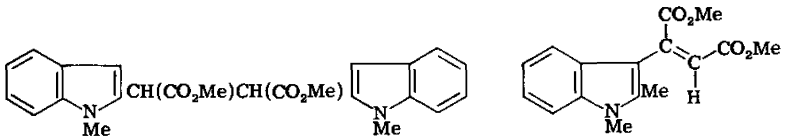
[23] W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Am. Chem. Soc.* **81**, 6010 (1959).

3-Tricyanovinylindole (**57**) and its 1-methyl derivative, obtainable from the parent indoles and tetracyanoethylene, combine with dimethyl acetylenedicarboxylate to give the corresponding carbazoles.[23] That derived from indole (**58**) has been hydrolyzed and esterified yielding (**55**).



[57] [58]

Dimethyl acetylenedicarboxylate with 1-methylindole is stated[21] to give the 2,2′-diindolylsuccinate (**59**), although the 3,3′-isomer is more likely and with 1,2-dimethylindole a 1:1 molar adduct was obtained.[24] It is described as the maleate (**60**) but may be the corresponding fumarate.

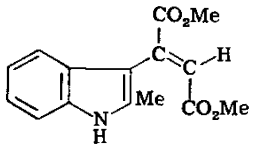


[59] [60]

2-Methylindole and acetylenedicarboxylic acid is reported[25] to give two unidentified products, but with the dimethyl ester the *cis* and *trans* (**61**) adducts were obtained. It was suggested that the major product had the *trans* configuration but this was not proved. Hydrogenation of both adducts gave the corresponding succinic ester, which was also obtained from 2-methylindole and maleic anhydride, followed by esterification.

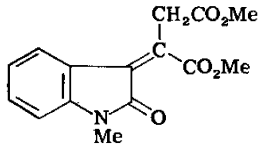
1-Methyloxindole and dimethyl acetylenedicarboxylate with methanolic sodium methoxide gave two addition products which from their ultraviolet absorption spectra are suspected[26] to be the geo-

[24] O. Diels, K. Alder, and W. Lübbert, *Ann. Chem. Liebigs* **490**, 277 (1931).
[25] R. F. Lange, *Dissertation Abstr.* **20**, 1172 (1959).
[26] J. A. Ballantine, R. J. S. Beer, and A. Robertson, *J. Chem. Soc.* p. 4779 (1958).



[61]

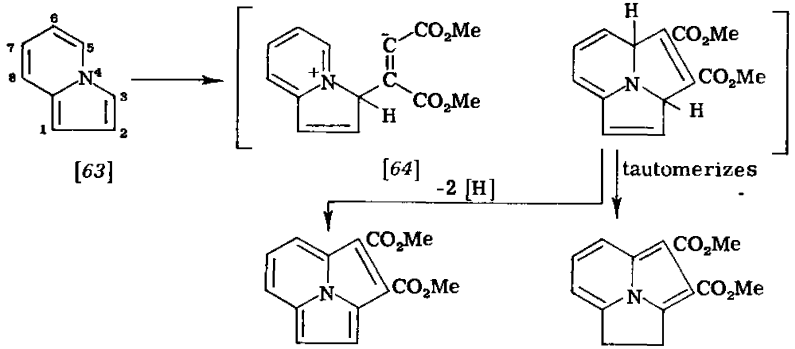
metrical isomers associated with (**62**), formed by a Michael addition and subsequent isomerization.



[62]

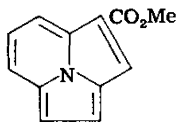
C. Indolizines

Boekelheide *et al.*[11,12] have recently shown that indolizine (**63**) and dimethyl acetylenedicarboxylate in hot toluene with palladium on charcoal yield dimethyl cycl[3.2.2.]azine-1,2-dicarboxylate (**65**) in 65–70% yield along with 10–15% of the corresponding 3,4-dihydro-derivative (**66**). The formation of these compounds can be accommodated on the scheme outlined. Molecular orbital calculations suggest that electrophilic attack at position 3 yielding (**64**) will take place in preference to a simultaneous attack at positions 3 and 5.



[63] [64] [65] [66]

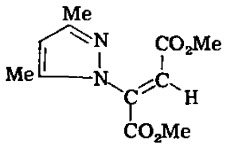
Similarly, methyl propiolate[27] and methyl phenylpropiolate[12] give the cyclazine (**67**) and its 2-phenyl derivative, respectively, as would be expected of reactions initiated through a Michael addition to the acetylenic ester.



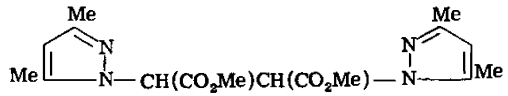
[67]

D. Pyrazoles

Pyrazole and its 3,5-dimethyl and 3,4,5-trimethyl derivatives combined[28] with two moles of dimethyl acetylenedicarboxylate giving products of similar ultraviolet absorption spectra to the parent pyrazoles. These products [e.g., (**69**)] do not possess the strong broad absorption at ca. 3.20 μ characteristic of the bonded N—H group which is present in the parent pyrazoles and are formed by two successive Michael addition reactions. In the case of 3,5-dimethylpyrazole, the initial fumarate (**68**) has been isolated and possessed a more conjugated type of absorption spectrum to those of the dipyrazolyl-



[68]



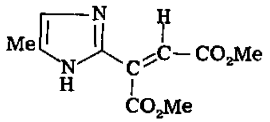
[69]

succinates (**69**). *N*-Substituted pyrazoles also react with the acetylenic ester but have so far yielded only tars.

[27] V. Boekelheide and T. Small, *J. Am. Chem. Soc.* **83**, 462 (1961).
[28] R. M. Acheson and P. W. Poulter, *J. Chem. Soc.* p. 2138 (1960).

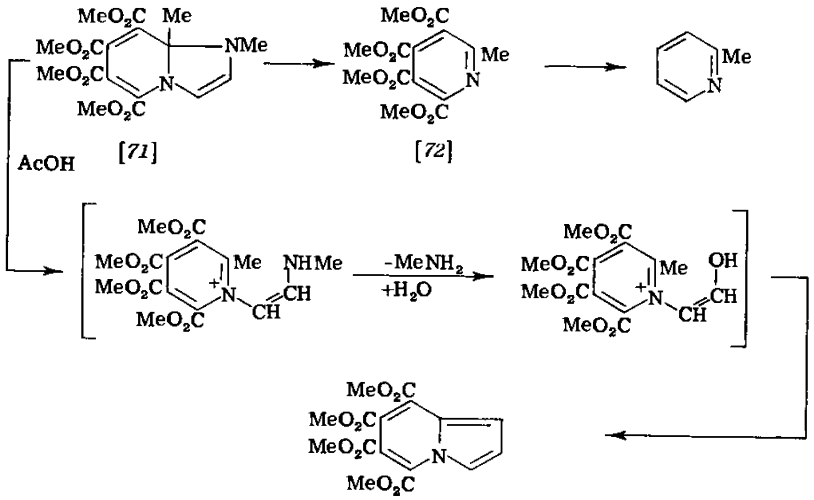
E. Imidazoles

Dimethyl acetylenedicarboxylate and 4-methylimidazole are reported[21] to yield dimethyl 5-methyl-2- (**70**) or -4-imidazolylmaleate; a fumarate might perhaps have been expected and no structure proof was given.



[70]

A different type of adduct (**71**) is obtained[21] from 1,2-dimethylimidazole and the ester. Its structure is fairly certain as oxidation with



[71] [72] [73]

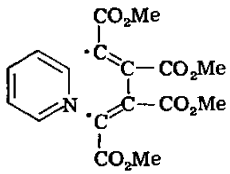
bromine and methanol gives a tetramethyl 2-methylpyridinetetracarboxylate (**72**) which has been hydrolyzed and decarboxylated to 2-methylpyridine; the formation of the pyridine tetraester, which has been confirmed,[10] excludes alternative formulations for the adduct

which could be suggested on analogy with the products obtained from 1-methylpyrrole and the acetylenic ester (Section III,A,2). The structure also accounts for the loss of methylamine and the formation of the indolizine (**73**) when the compound is treated with glacial acetic acid.

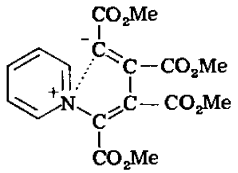
F. Pyridines

1. *Pyridine and Alkylpyridines with Dimethyl Acetylenedicarboxylate in Ether near Room Temperature*

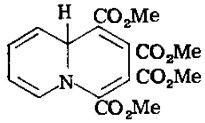
Pyridine,[29] and its monomethyl and 3,5-dimethyl derivatives[14] combine exothermically with dimethyl acetylenedicarboxylate in ether yielding some ether soluble materials, including trimethyl pyrrocoline-1,2,3-tricarboxylate (Section III,F,3) and deep red ether-insoluble gums. A number of crystalline compounds have been isolated from these gums by fractional crystallizations and will now be considered in detail. In the case of pyridine, Diels *et al.*[29] isolated a red "labile"[29a] 1:2 molar adduct, which they formulated as (**75**), which isomerized rapidly on standing to a yellow "stable" adduct (**76**). These formulations are no longer accepted. Diels and Alder also suggested that the acetylenic ester first dimerized to the diradical (**74**) which then combined with the pyridine.



[74]



[75]



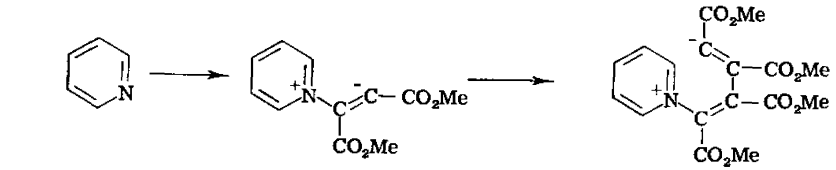
[76]

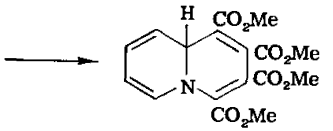
a. 9aH-Quinolizines, or the "Labile" Adducts. The labile adduct of pyridine with two moles of dimethyl acetylenedicarboxylate [tetramethyl 9a*H*-quinolizine-1,2,3,4-tetracarboxylate (**77**)], obtained by Diels *et al.*,[29] has not been described by later workers and it rapidly

[29] O. Diels, K. Alder, T. Kashimoto, W. Friedrichson, W. Ekhardt, and H. Klare, *Ann. Chem. Liebigs.* **498**, 16 (1932), and later papers.

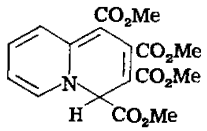
[29a] In this chapter the words "labile" and "stable" are used in a special context; they derive their meaning from the original German papers and in fact refer to 9a*H*- and 4*H*-quinolizine derivatives respectively.

isomerized to the stable isomer (tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (**78**), which is the usual product isolated from the reaction. Corresponding labile adducts, obtained from 3-methylpyridine (one of the two possible isomers only),[14] 3,5-dimethylpyridine,[14] and various benzopyridines, are stable enough to be prepared





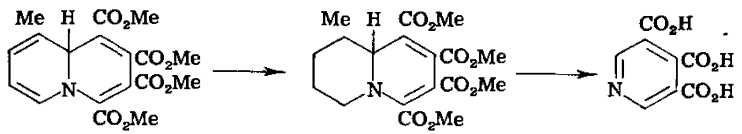
[77]



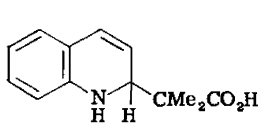
[78]

easily and do not isomerize at room temperature. The mechanism of the addition is readily accommodated on a stepwise addition of two molecules of the ester to the pyridine, and, although not rigorously proved, it seems probable that this sequence is followed for the reason given in Section II.

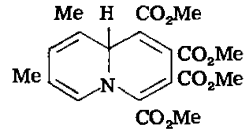
The bicyclic nature of the labile adduct (**79**) from 3-methylpyridine was established by Acheson and Taylor[14] who found that hydrogenation, yielding (**80**), followed by oxidation gave pyridine-3,4,5-tricarboxylic acid. This conclusion is consistent with Diels and Alder's observations that acid hydrolysis of the labile pyridine adduct gave pyridine and some crotonaldehyde, whereas alkaline hydrolysis yielded pyridine, oxalic acid, and aconitic acid. The dihydroquinoline (**81**) gives quinoline and isobutyric acid on similar alkaline hydrolysis.[30]



[79] [80]



[81]



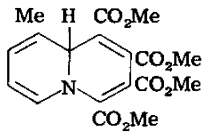
[82]

The 9a*H*-quinolizine structure (**82**) for the labile adduct from 3,5-dimethylpyridine was clearly established by the nuclear magnetic resonance studies of Richards and Higham,[31] and subsequent work showed the labile adduct from 3-methylpyridine was analogous.[32] As the labile adducts from all the pyridines and benzopyridines so far examined have very similar infrared absorption spectra in the 5–7 μ (carbonyl and aromatic) region[33] and within quite close limits very similar ultraviolet absorption spectra, it can be concluded that all are derivatives of 9a*H*-quinolizine.

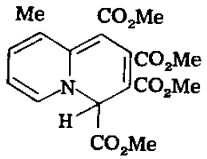
The ease of isomerization of the labile adducts, the 9a*H*-quinolizines, to their stable tautomers, the 4*H*-quinolizines, varies enormously. The labile pyridine adduct (**77**) was definitely obtained by Diels and Alder, although later attempts to obtain it have given only the stable isomer, as the ultraviolet absorption spectrum recorded[29] is similar to those of the labile adducts of 3-methyl- and 3,5-dimethylpyridine. 3-Methylpyridine and dimethyl acetylenedicarboxylate gave a mixture of the 9-methyl-9a*H*- and -4*H*-quinolizines, (**83**) and (**84**), and the 7-methyl-4*H*-quinolizine (**86**); none of the 7-methyl-9a*H*-quinolizine (**85**) was isolable. 3,5-Dimethylpyridine and the ester yields the 7,9-dimethyl-9a*H*-quinolizine (**82**) which like the 9-methyl-9a*H*-quinolizine (**83**) is converted to the corresponding 4*H* isomer by boiling in benzene or treating with strong acids. This suggests that steric hindrance in the region of the 9a*H*-hydrogen atom stabilizes this type of compound.

Isomerization could occur through the addition and loss of a proton

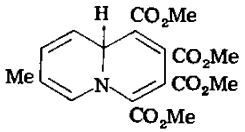
[30] H. Staudinger, H. W. Klewer, and P. Kober, *Ann. Chem. Liebigs* **374**, 1 (1910).
[31] See Appendix in reference 14.
[32] L. M. Jackman, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.* p. 1579 (1960).
[33] R. M. Acheson and F. Hole, *J. Chem. Soc.* p. 748 (1962).



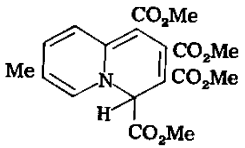
[83]



[84]



[85]



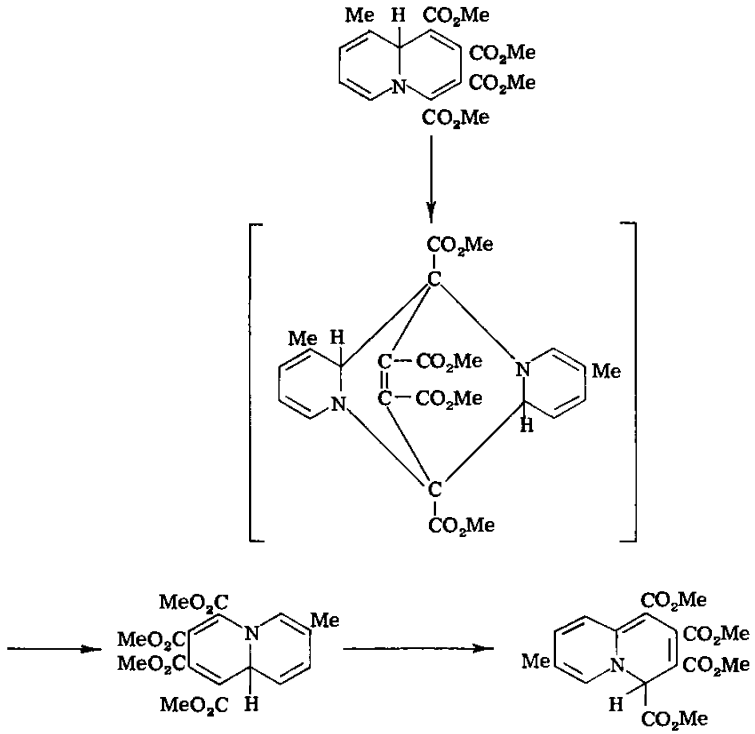
[86]

but as 9a*H*-quinolizines do not form salts with perchloric acid, this is probably not the usual mechanism. A 1,3-shift of the 9a-hydrogen atom or its loss as a hydride ion leaving a dehydroquinolizinium cation which is then attacked by the hydride anion at position 4, as is the case with the methoxide anion (Section III,F,1,c), are other possibilities.

Heating the 9-methyl-9a*H*-quinolizine (**83**) with 2-methylpyridine in methanol causes isomerization to the corresponding 9-methyl-4*H*-quinolizine (**84**), but with 3-methylpyridine the isomeric 7-methyl-4*H*-quinolizine (**86**) is obtained.[32] Similarly the 9-methyl compound (**83**) and the corresponding 7,9-dimethyl derivative (**82**)[22] with pyridine yield tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (**78**) with loss of the original alkylated pyridine. The mechanism of these reactions has not been established but the addition–elimination isomerization sequence for 3-methylpyridine accounts for the known cases of exchange of the pyridine (see Scheme 1).

b. 4H-Quinolizines, or the "Stable" Adducts. 4*H*-Quinolizines are often present in the mixtures obtained from pyridines and dimethyl acetylenedicarboxylate and can also be obtained from the isomeric 9a*H*-quinolizines as just described.

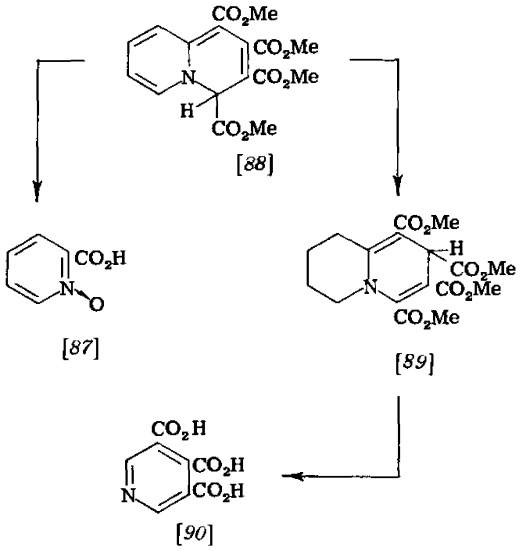
Diels *et al.*[29] oxidized the stable pyridine adduct, tetramethyl 4*H*-



Scheme 1

quinolizine-1,2,3,4-tetracarboxylate (**88**) with hydrogen peroxide and acetic acid to pyridine-2-carboxylic acid *N*-oxide (**87**), thereby proving the presence of this structural grouping of carbon and nitrogen atoms in the adduct. As the ultraviolet absorption spectrum of the adduct showed more conjugation than that present in the corresponding 9a*H*-quinolizine and as the adduct formed a salt in 60% sulfuric acid and absorbed four moles of hydrogen under these conditions, Woodward and Kornfeld[3] concluded that it must have the bicyclic structure (**88**). Independently, but much later, Acheson and Taylor[14] confirmed the hydrogen peroxide–acetic acid oxidation of the adduct and showed that hydrogenation under neutral conditions gave first a tetrahydro derivative (**89**) and finally an octahydro derivative. Oxidation of the tetrahydro derivative (**89**), the structure of which had

been deduced from its ultraviolet and nuclear magnetic resonance spectra, gave pyridine-3,4,5-tricarboxylic acid (**90**). These observations are difficult to account for except on the basis of a bicyclic structure.



[*88*]

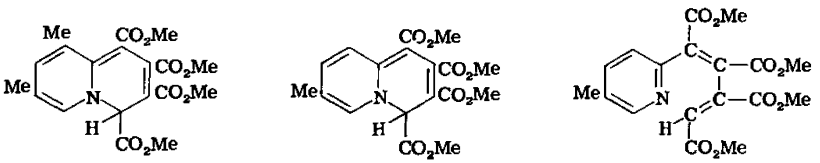
[*87*]

[*89*]

[*90*]

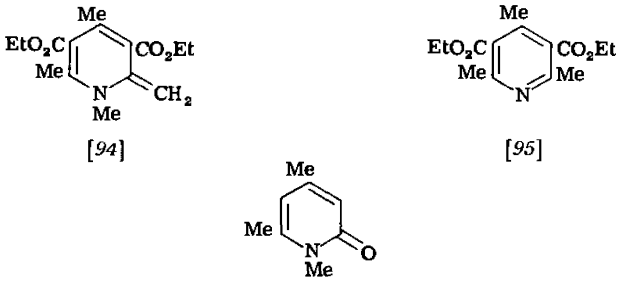
The nuclear magnetic resonance spectrum of tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (**91**) showed that a hydrogen atom was present at position 4.[31] Elvidge and Jackman[34] have suggested that nuclear magnetic resonance spectroscopy cannot distinguish between formulations (**92**) and (**93**) for one stable adduct from 3-methylpyridine. They state that to accommodate the chemistry it is possible to formulate the stable adducts as a mixture of ring-chain tautomers [e.g., (**92**) and (**93**)] in which case the equilibrium must be very rapidly established and must be well toward (**93**). This conclusion derives from the observation that the τ value of the methyl protons of one of the "stable" adducts from 3-methylpyridine [(**92**), an incorrect formulation is given in the original paper] indicates the presence of a ring current, as was previously observed for the stable adduct (**91**) from 3,5-dimethylpyridine. It was

[31] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* p. 859 (1961).



[*91*] [*92*] [*93*]

also shown,[34] on the same criterion, that the "nonaromatic" pyridine (**94**) possessed virtually no ring current in comparison with the substantial current present in the corresponding pyridine (**95**) and that similar pyridones [e.g., (**96**)] possess a ring current which is less than that of the parent pyridines. The conclusion that the stable adduct cannot have the bicyclic structure (**92**) analogous to (**94**) as it does



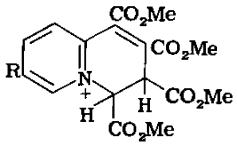
[*94*] [*95*]

[*96*]

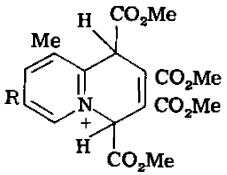
possess a substantial ring current, does not necessarily follow as the adduct is a vinylogous pyridone in two senses. It would, therefore, be expected to possess a ring current in the aromatic region as regards magnitude, which it does. The suggestion that a rapidly attained tautomerism pertains is not easy to reconcile with the hydrogenation data for the pyridine adduct (**88**), the formation of (**138**) in the oxidation of the stable phenanthridine adduct, nor with the protonation data to be discussed next. However it is worth noting that some attempts[35] to prepare quinolizine itself have yielded 2-(1-butadienyl)-pyridine; it is possible that the extra conjugation provided by the many ester groups stabilizes the bicyclic system in the preceding adducts.

[35] V. Boekelheide and W. G. Gall, *J. Am. Chem. Soc.* **76**, 1832 (1954); V. Boekelheide and J. P. Lodge, *J. Am. Chem. Soc.* **73**, 3681 (1951).

The stable adducts form salts with perchloric acid in methanol and the ultraviolet absorption spectra of these salts fall into two classes.[14] The spectra of the cations from both tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate and its 7-methyl derivative are very similar and closely resemble that of 3,4-dihydroquinolizinium iodide. This strongly suggests that the proton has added at position 3 yielding cations such as (**97**).



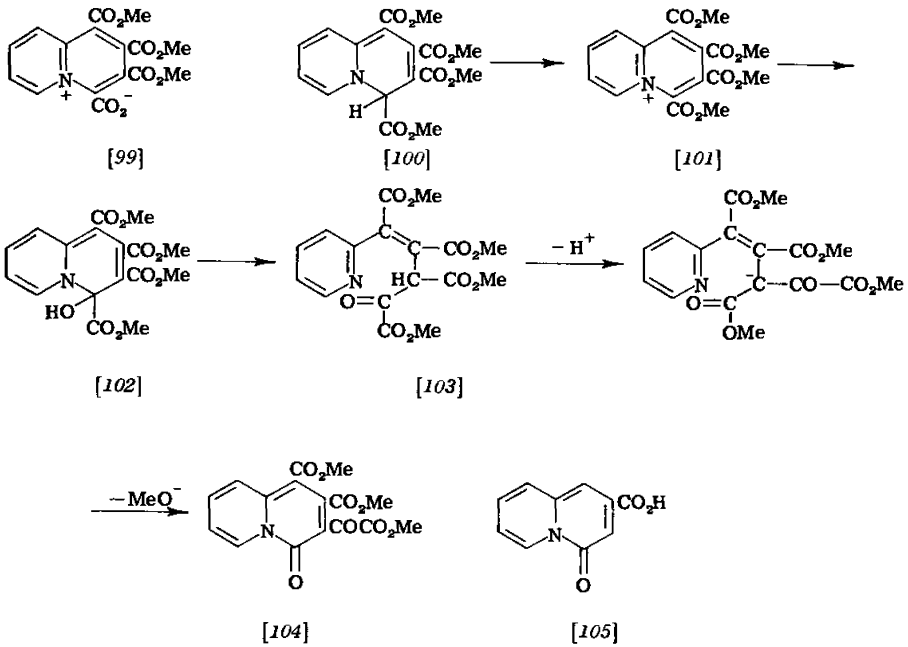
[*97*]



[*98*]

The spectra of the cations derived from the isomeric 9-methylquinolizine (**84**) and its 7-methyl derivative (**91**) are closely similar and are consistent with an unconjugated pyridinium structure. In these cases the proton must add largely at position 1, giving (**98**). It is difficult to account for this change in orientation except on the basis that there is considerable steric strain between the substituents at positions 1 and 9, that this is reduced by making the 1-carbon atom tetrahedral, and that the strain is so great as to make a reduction preferred to a retention of conjugation. If these adducts were largely in the open chain form, it would be difficult both to understand why protonation of the nitrogen atom should not occur and to account for the different types of cation which can be formed.

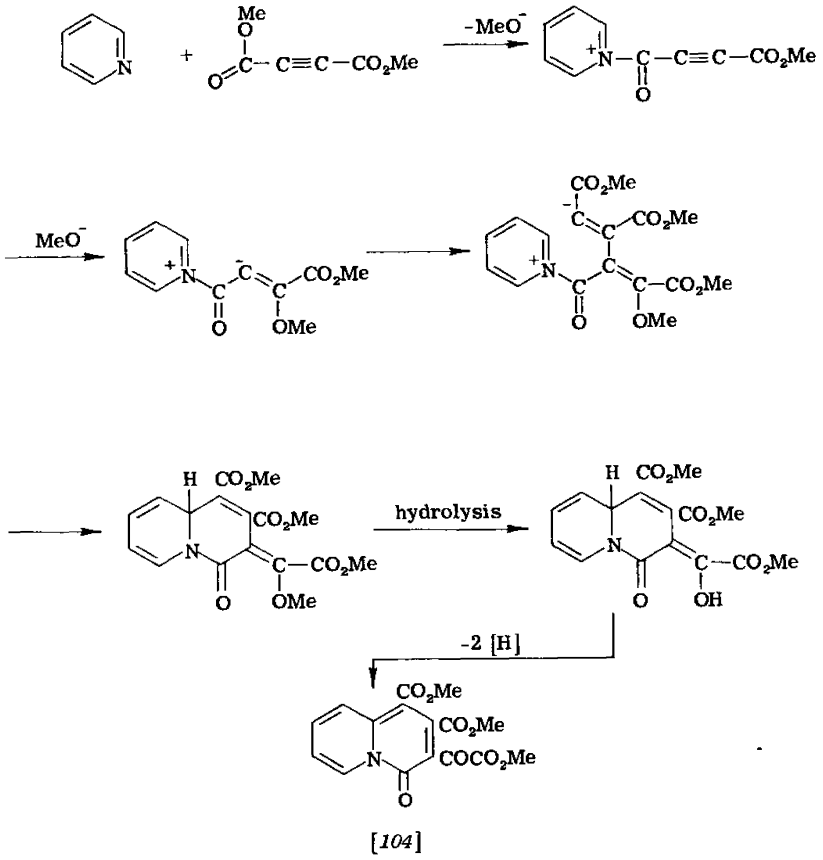
c. "Kashimoto's Compound." "Kashimoto's compound" is a minor product of the reaction between dimethyl acetylenedicarboxylate and pyridine; a homolog is obtained from 3-methylpyridine.[32] It was originally formulated as (**99**) but Woodward and Kornfeld[3] have shown that it actually possesses structure (**104**), since with warm concentrated sulfuric acid it yields a compound identical with authentic quinoliz-4-one-2-carboxylic acid (**105**). Infrared and ultraviolet absorption data[14] are consistent with the new formulation. It was suggested[3] that the compound was formed through oxidation of the first-formed pyridine stable adduct (**100**) *in situ* to the dehydroquinolizinium cation (**101**) followed by addition of a hydroxyl anion at position 4. The resulting carbinolamine (**102**) will be in equilibrium with the corresponding keto ester (**103**), which through loss of the elements of methanol can give Kashimoto's compound (**104**). The first two stages of this scheme are supported by the observations that *N*-bromosuccinimide oxidizes the stable adduct (**100**) to the quinolizinium (**101**) bromide and subsequent treatment with methanolic sodium methoxide gives a solution of ultraviolet absorption spectrum very similar to that of the parent adduct (**100**), thereby indicating the addition of the methoxide ion at position 4 [cf. structure (**102**)].[14]



[*99*] [*100*] [*101*] [*102*] [*103*] [*104*] [*105*]

An alternative scheme which has parallels with several reactions described in Section II can also account for the production of Kashimoto's compound and is outlined in the following. Initial attack of the pyridine nitrogen atom on the ester group with the expulsion of

a methoxide ion is postulated and is similar to the reaction of pyridine with benzoyl chloride. Subsequent addition of the methoxide ion to the triple bond is oriented by the positively charged nitrogen atom, and reaction with another mole of the acetylenic ester is followed by cyclization. Hydrolysis of the resulting enol methyl ether and dehydrogenation to Kashimoto's compound (**104**) may then take place (see Scheme 2).

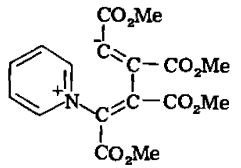


[*104*]

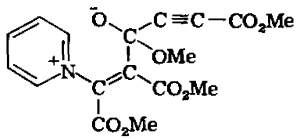
Scheme 2

2. *Pyridine and Alkylpyridines with Dimethyl Acetylenedicarboxylate in Ether at Low Temperatures*

When pyridine and 3-methylpyridine are treated with dimethyl acetylenedicarboxylate in ether or toluene at −50 to −10°C, Jackman *et al.*[32] found that very unstable cream colored solids are precipitated which analyze approximately for 1:2 molar adducts. On standing at room temperature the adduct from 3-methylpyridine gave carbon dioxide and a dark resin, from which 3-methylpyridine and small amounts of tetramethyl 7-methyl-4*H*- (**86**) and 9-methyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylates (**83**) were isolated; the pyridine adduct was similar and gave a little (**100**). Traces of dimethyl fumarate and of a compound which was not identified were also detected. The analytical and ultraviolet data for the last compound and its hydrolysis product, however, strongly suggest that it was dimethyl methoxy-fumarate (or -maleate) as previously isolated from the same reaction carried out with methanol (Section III,F,3). These authors[32] suggested that a true ylide structure (**106**) was possible for the adduct. This seems unlikely as the yields of the cyclic quinolizines obtained on standing were very small, and it is known that the carbanion derived from methyl propiolate combines easily with pyridinium derivatives at position 2 (Section III,F,4). The low-temperature adduct from pyridine and others from related bases possess a very strong acetylenic-type absorption in the infrared and it is, therefore, suggested[22] that this adduct may have structure (**107**)



[*106*]



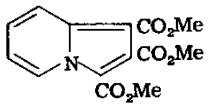
[*107*]

related to and formed in a similar way to the phenanthridine adduct (**139**). Equilibria between *N*-alkylpyridinium hydroxides and the corresponding 2-hydroxy-1,2-dihydropyridines strongly favor the ionic structures,[36] whereas the reverse is true for certain phenanthridines.[37] The instability of the adduct (**107**), because of attack of methoxide anion on the highly activated acetylenic side chain, would be expected.

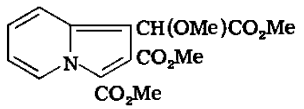
3. *Pyridine and Dimethyl Acetylenedicarboxylate in Methanol*

Diels and Meyer[16] found that the exothermic reaction obtained on dropping pyridine into dimethyl acetylenedicarboxylate in methanol gave a mixture of the indolizine (**108**) and a methoxymethylindolizine formulated as (**109**), and some dimethyl fumarate and dimethyl methoxyfumarate. Later workers[17,38] obtained only the methoxymethylindolizine in rather poor yield. The indolizine (**108**) has also been isolated from the products obtained when the addition reaction was carried out in ether, but in this case the course of the reaction was very susceptible to the presence of impurities in the ether, and the results indicated that ethanol was necessary as a reactant.[39]

Crabtree, Johnson, and Tebby then showed that the methoxymethylindolizine, originally formulated as (**109**), on successive treatment with hydrogen iodide and diazomethane gave (**110**). The methoxymethylindolizine must, therefore, be (**111**) and a similar compound was obtained from 3-methylpyridine. Attempts to convert corresponding labile (**77**) and stable adducts (**78**) into (**111**) by

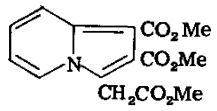


[*108*]

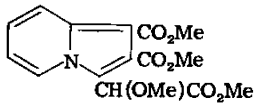


[*109*]

[36] R. M. Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," p. 164. Interscience, New York, 1960.
[37] R. M. Acheson and G. J. F. Bond, *J. Chem. Soc.* p. 246 (1956).
[38] E. T. Burrows and D. O. Holland, *J. Chem. Soc.* p. 672 (1947).
[39] R. H. Wiley and L. H. Knabeschuh, *J. Org. Chem.* **18**, 836 (1953).



[*110*]

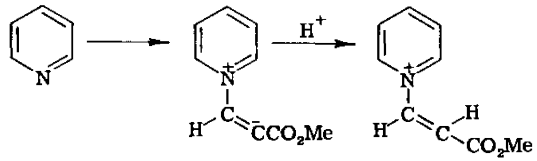


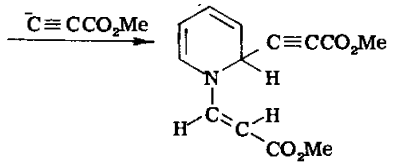
[*111*]

treatment with methanol alone or with sodium methoxide or hydrochloric acid were unsuccessful, and the formation of indolizines in the original reaction was not accounted for. A mechanism[15] which explains the formation both of (**108**) and of (**111**) and which includes methanol as a reactant is given in Section II,D,3.

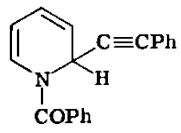
4. *Pyridine and Methyl Propiolate*

Methyl propiolate and pyridine give a rather unstable 2:1 molar adduct which is the 1,2-dihydropyridine (**112**).[17] The reaction sequence proposed to account for its formation is identical in principle to a similar scheme proposed earlier in the acridine series (Section II,A,2) and is also supported by the observation that the 1-benzoylpyridinium cation with the phenylacetylide anion yields (**113**).[40]





[*112*]



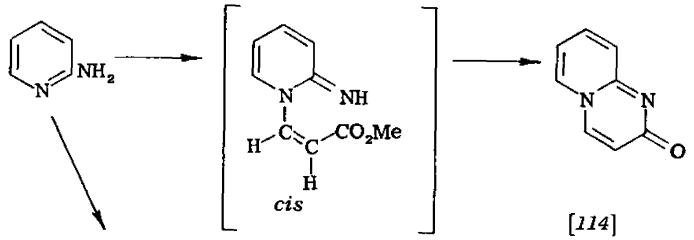
[*113*]

5. *2-Aminopyridines and Methyl Propiolate*

Methyl propiolate and 2-aminopyridine in ether gave a mixture of

[40] T. Agawa and S. I. Miller, *J. Am. Chem. Soc.* **83**, 449 (1961).

2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**114**) and (**116**).[41] Other 2-aminopyridines behave similarly and in some instances the *trans* intermediate [cf. (**115**)] was isolated.

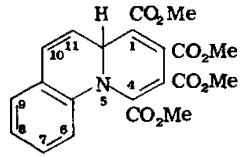


[*114*]

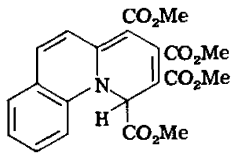
[*115*] [*116*]

G. Quinoline and Dimethyl Acetylenedicarboxylate

Quinoline,[42] like pyridine, and the ester give a 1:2 molar labile adduct (**117**) which is not basic and isomerizes on heating or with acids to a stable isomer (**118**) as in the pyridine series. It has been

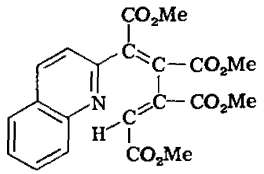


[*117*]



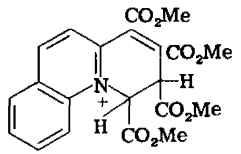
[*118*]

[41] G. R. Lappin, *J. Org. Chem.* **26**, 2350 (1961).
[42] O. Diels and K. Alder, *Ann. Chem. Liebigs* **510**, 87 (1934).



[*119*]

suggested,[43] on the basis of the nuclear magnetic resonance spectra of (**117**), its 11a-methyl derivative obtained from 2-methylquinoline, and the stable adduct (**118**), that the last compound could be better represented in the open-chain form (**119**). However these spectra can be interpreted in an alternative way[44] and are then not inconsistent with the tricyclic structure (**118**). This is further supported by the ultraviolet spectra of the adduct in neutral and in acid solution. Acid causes a hypsochromic shift of the long-wavelength maxima of ca. 980 Å and strongly suggests that a proton is added at position 3 yielding (**120**). This may be compared with similar cations [e.g., (**97**)] obtained from pyridine adducts.

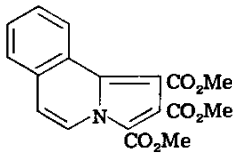


[*120*]

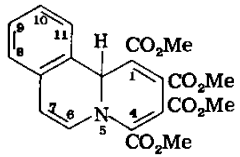
H. Isoquinoline and Dimethyl Acetylenedicarboxylate[33]

In methanol, isoquinoline and the ester gave the benzo[*g*]indolizine [(**121**), cf. Section II,D,3] while in ether the labile adduct, tetramethyl 11b*H*-benzo[*a*]quinolizine-1,2,3,4-tetracarboxylate (**122**) was obtained. The labile adduct is much less easily isomerized than the 9-methyl-9a*H*-quinolizines derived from pyridines (Section III,F,1) but with boiling xylene or, better, with sulfuric–acetic acids the cor-

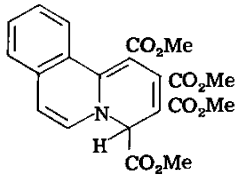
[43] E. E. van Tamelen, P. E. Aldrich, P. Bender, and G. Miller, *Proc. Chem. Soc.* p. 309 (1959).
[44] R. M. Acheson, N. J. Earl, P. Higham, R. E. Richards, G. A. Taylor, and J. M. Vernon, *Proc. Chem. Soc.* p. 281 (1960).



[121]

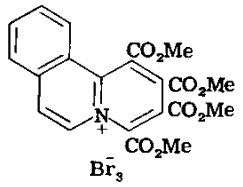


[122]

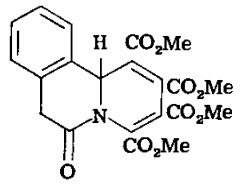


[123]

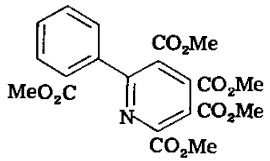
responding stable adduct, tetramethyl 4*H*-benzo[*a*]quinolizine-1,2,3,4-tetracarboxylate (**123**) is obtained. Oxidation of the stable adduct (**123**) with bromine in methanol gave the benzoquinolizinium perbromide (**124**), but a similar oxidation of the labile adduct yields first (**125**) and subsequently the pyridine (**126**). This difference in behavior contrasts with the pyridine labile and stable adducts where both types are converted by bromine to the same quinolizium salt. Possibly the labile adduct is first isomerized to the stable isomer by the reaction mixture, whereas in the isoquinoline series the labile isomer is unchanged under these conditions which then permits the alternative reaction to occur. Hydrogenation of the labile adduct over palladium on charcoal gave a dihydro derivative (**127**), whereas



[124]



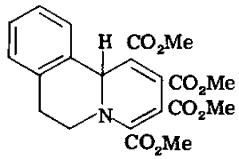
[125]



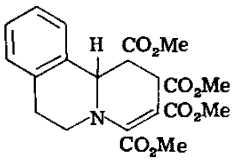
[126]

with Raney nickel a mixture of two tetrahydro derivatives was obtained. One of the tetrahydro derivatives was identical with the

product obtained from the stable adduct with hydrogen over platinic oxide. The structure suggested for the dihydro (**127**) and tetrahydro derivatives (**128**) (including various geometrical isomers) were deduced from ultraviolet absorption spectrum comparisons.



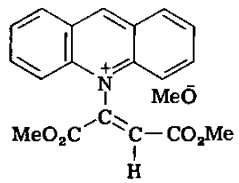
[127]



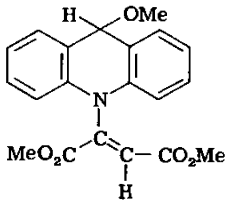
[128]

I. Acridine and Dimethyl Acetylenedicarboxylate[5]

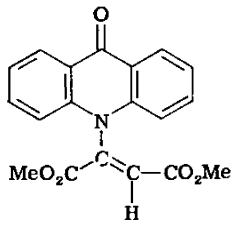
Acridine and the ester in the presence of hot excess methanol, partially used as solvent, combine readily giving a high yield of the 1:1:1 molar *trans* adduct (**129**), and it was suggested that the reaction was analogous to the well-known Michael addition reaction which usually gives *trans* products. The adduct is in equilibrium with the corresponding 9,10-dihydroacridine (**130**) and oxidation with air or hydrogen peroxide yields the corresponding acridone (**131**).



[129]



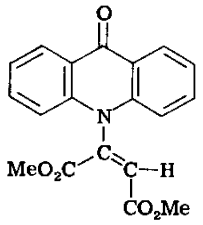
[130]



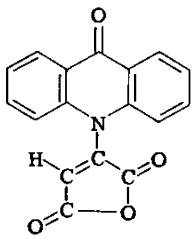
[131]

Hydrogenation of the acridone over Raney nickel gave acridone itself and dimethyl fumarate.

When acridine and the ester were left in ether at room temperature, aerial oxidation presumably occurred giving a mixture of the maleate (**132**) and fumarate (**131**) in roughly equal proportions. The stereochemistry of these adducts was established through hydrolysis to the corresponding acids which with refluxing acetic anhydride gave the same anhydride (**133**). Hydrolysis of this last anhydride gave the maleic acid, which was identical with one of the original hydrolysis products.



[*132*]

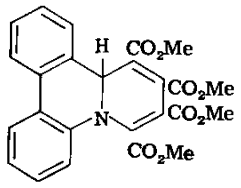


[*133*]

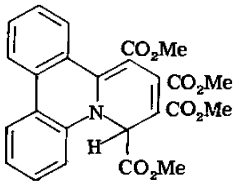
J. Phenanthridine and Dimethyl Acetylenedicarboxylate

1. *In Benzene*[15]

The major product of this reaction is the yellow, labile, 1:2 molar adduct (**134**) corresponding to the pyridine series, along with a small amount of a colorless compound (**139**) which is discussed later and some phenanthridine oxalate. The labile adduct is converted to the stable isomer (**135**) on heating in quinoline or pyridine. Oxidation of both these adducts with potassium permanganate in acetone gives phenanthridone as the major product. In the case of the labile adduct,

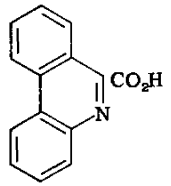


[*134*]

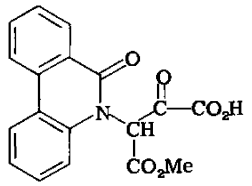


[*135*]

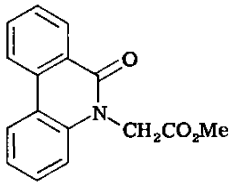
some phenanthridine-6-carboxylic acid (**136**) and N-substituted phenanthridone derivatives were detected, indicating the positions of addition to the phenanthridine system. Several N-substituted phenanthridones were obtained as minor products from the stable adduct oxidation and two have been positively identified as (**137**) and (**138**). This is consistent with the structure proposed (**135**) for the stable adduct but could not be readily accounted for on an open-chain type structure [cf. (**93**) and (**119**)].



[*136*]

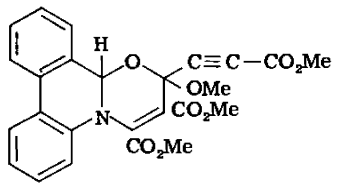


[*137*]

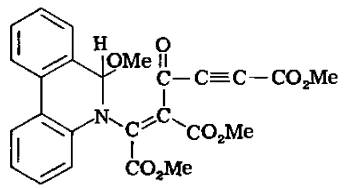


[*138*]

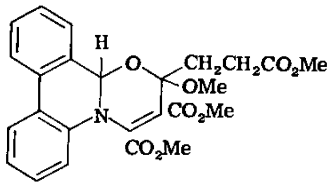
The colorless compound obtained from the original reaction between phenanthridine and the ester is a 1:2 molar adduct (**139**) of a new type, and is probably formed as indicated in Section II,D,2. Oxidation gave mainly phenanthridone. The ultraviolet absorption spectrum of the adduct is very similar to that of (**142**), and its infrared absorption spectrum shows the presence of the acetylenic bond possessing a terminal ester group. There is no absorption near 6 μ, so an alternative formulation (**140**) which possesses a conjugated carbonyl group can be excluded. Two moles of hydrogen are taken up on careful catalytic hydrogenation, and the infrared absorption characteristic of the acetylenic bond and associated ester group disappears. The nuclear magnetic resonance spectrum of this tetrahydro



[*139*]



[*140*]

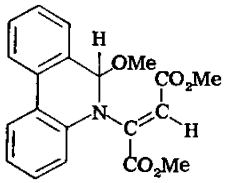


[141]

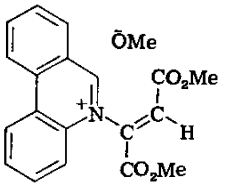
derivative (**141**) shows the presence both of the methylene groups and of the isolated proton.

2. *In Methanol*[37]

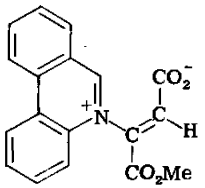
Like acridine, phenanthridine and dimethyl acetylenedicarboxylate in methanol give a high yield of 1:1:1 molar adduct. Ultraviolet absorption spectrum comparisons show that this is best formulated as 9,10-dihydro-9-methoxy-10-(*trans*-1,2-dimethoxycarbonylvinyl)phenanthridine (**142**) rather than the corresponding phenanthridinium methoxide (**143**) under neutral conditions; acidification changes the spectrum to that characteristic of the phenanthridinium cation. Crystallization of the adduct (**142**) from methanol containing 5–15% of water gave the betaine [(**144**); the positions of the ester and carboxylate groups have not been established], while in the presence



[142]

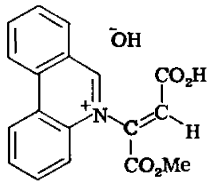


[143]

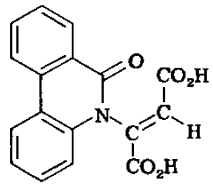


[144]

of more water the hydroxide (**145**) is formed. Oxidation and hydrolysis of the betaine (**144**) with alkaline potassium ferricyanide gave the phenanthridone (**146**). It has the *trans* structure, as cyclization to the anhydride followed by hydrolysis gave an isomeric *cis* acid.



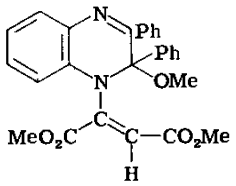
[145]



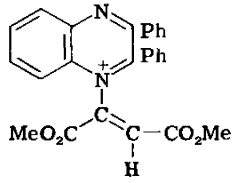
[146]

K. Quinoxalines and Dimethyl Acetylenedicarboxylate

2,3-Diphenylquinoxaline and dimethyl acetylenedicarboxylate in methanol,[45] as in the phenanthridine case, combined to give a yellow pseudomethoxide (**147**) converted by acid into the corresponding quinoxalinium salt (**148**). Heating the adduct (**147**) with ethanolic potassium hydroxide gave 45% 2,3-diphenylquinoxaline, along with



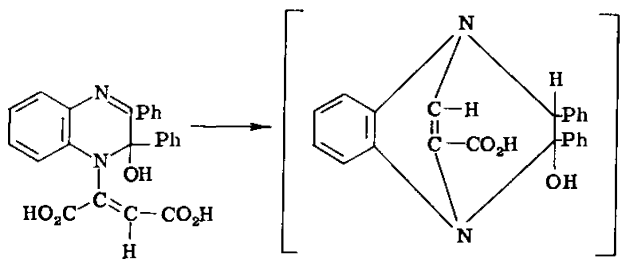
[147]



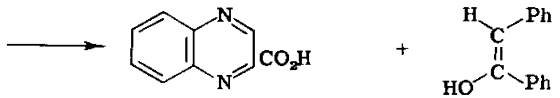
[148]

16% deoxybenzoin, 17% quinoxaline-2-carboxylic acid, and 23% carbon dioxide. The similarity in yield of the last three compounds suggests that they are all formed in the same reaction. Assuming that the ester groups in the adduct (**147**) are *trans*, a fact which has not been proved but which is the case with corresponding acridine and phenanthridine adducts, a scheme can be proposed to account for the results. Decarboxylation of the hydrolyzed adduct, in which the 2-methoxyl had been exchanged for a 2-hydroxyl (**149**) β to the nitrogen atom, would have to occur before transannular attack and addition of a proton could lead to the hypothetical intermediate (**150**). Scission as indicated would give the (aromatic) quinoxaline-2-carboxylic acid (**151**) and the enolic form (**152**) of deoxybenzoin.

[45] E. Grovenstein, W. Postman, and J. W. Taylor, *J. Org. Chem.* **25**, 68 (1960).

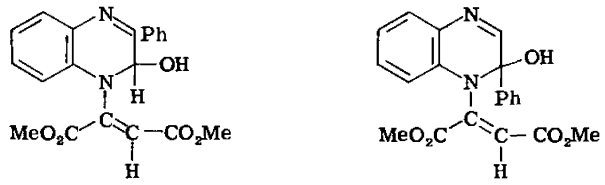


[149] [150]



[151] [152]

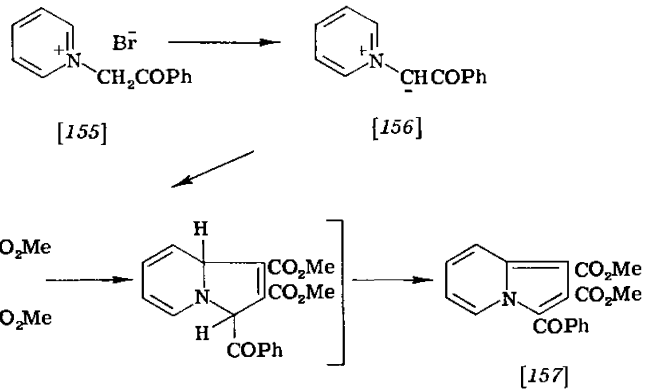
2-Phenylquinoxaline[45] behaves like 2,3-diphenylquinoxaline in giving a 1:1:1 molar adduct with the ester and methanol. The adduct is thought to possess structure (**153**) rather than the isomeric one (**154**).



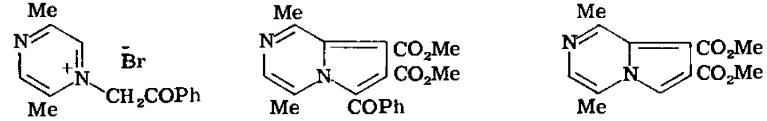
[153] [154]

L. Zwitterions Derived from Pyridine, Pyrazine, Isoquinoline, and Dimethyl Acetylenedicarboxylate

1-Phenacylpyridinium bromide (**155**) with aqueous sodium carbonate yields the chloroform soluble zwitterion (**156**) which, with dimethyl acetylenedicarboxylate in the presence of palladium on charcoal, cyclized to the indolizine (**157**) in ca. 20% yield.[13] In a similar way[13] the pyrazine (**158**) gave a mixture of (**159**) and (**160**) through loss of the benzoyl group. The last compound was also obtained in 1% yield from the acetylenic ester and the zwitterion obtained from 1,2,5-trimethylpyrazinium iodide and alkali.

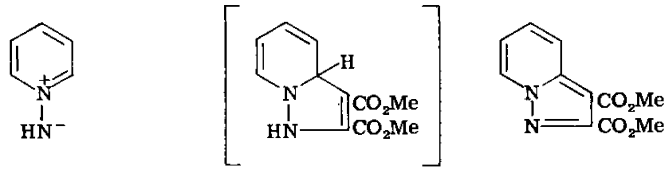


[155] [156] [157]



[158] [159] [160]

The imine (**161**), obtained from 1-aminopyridinium iodide and potassium carbonate, combines with dimethyl acetylenedicarboxylate yielding in the first place (**162**) which then with more ester gives dimethyl fumarate and the pyrazolopyridine (**163**), isolated in 15% yield.[46] A corresponding reaction with isoquinoline imine gave 75% of the primary adduct [(cf. (**162**)].[46]



[161] [162] [163]

Acknowledgments

I thank Mr. A. O. Plunkett, Dr. G. A. Taylor and Dr. J. M. Vernon for reading the manuscript and proofs.

[46] R. Huisgen, *Proc. Chem. Soc.* p. 357 (1961).

Heterocyclic Pseudo Bases

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I. Introduction

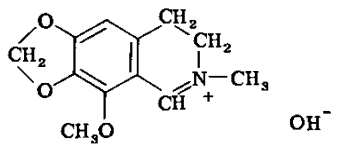
Hantzsch[1,2] gave the name "pseudo bases" to those carbinols that gave salts with acids by the elimination of water and a simultaneous change of constitution. Such carbinols are common among the nitrogen heterocyclic compounds and the naturally occurring alkaloids e.g., berberine, sanguinarine, chelerythrine.

The structure, and the mechanism of the chemical transformations, of the pseudo ammonium bases[3] which can be obtained from heterocyclic quaternary ammonium salts has been one of the most discussed phenomena in theoretical organic chemistry[4] since the first publication in this field by Claus and Himmelmann.[5] These questions have still not been finally decided.

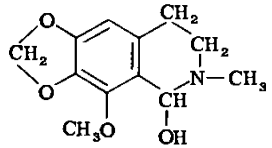
Recently Gadamer's view[6,7] has been widely accepted. He postulates for these compounds a tautomeric system of three components, in which the quaternary ammonium hydroxide, the pseudo base (or

[1] A. Hantzsch, *Ber. deut. chem. Ges.* **32**, 575 (1899).
[2] A. Hantzsch and M. Kalb, *Ber. deut. chem. Ges.* **32**, 3109 (1899).
[3] In addition, pseudobasic carbinols are known with oxygen (oxonium pseudo bases) or with sulfur as hetero atom (sulfonium pseudo bases).
[4] For early literature see V. Meyer and P. Jacobson, "Lehrbuch der organischen Chemie," Vol. II/3, p. 927, footnote 1. Walter de Gruyter, Berlin and Leipzig, 1920.
[5] A. Claus and P. Himmelmann, *Ber. deut. chem. Ges.* **13**, 2045 (1880).
[6] J. Gadamer, *Arch. Pharm.* **243**, 12 (1905).
[7] J. Gadamer, *J. prakt. Chem.* **84** (2), 817 (1911).

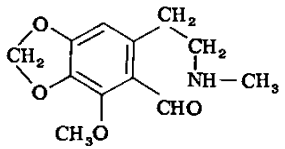
carbinolamine),[8,9] and the open-chain amino-aldehyde[10,11] all exist in a mobile equilibrium. Thus, cotarnine, a typical and the most investigated example of this class, would be considered as an equilibrium mixture of the three compounds (**1**), (**2**), and (**3**).



[*1*]



[*2*]



[*3*]

However, a critical examination of the enormous amount of the experimental material that has piled up over more than 80 years leads to the conclusion that the three tautomeric forms postulated by Gadamer have not been proven in one single case. The so-called evidence is based on chemical reactions,[10–15] which are noncompelling, or on physical constants that have been interpreted in a biased manner.[16] For the simultaneous existence of both forms of the ring-chain prototropic system, i.e., the carbinolamine and the amino-aldehyde, evidence is available only for one single case.[17]

The situation is similar for the derivatives obtained from the bases by the action of various nucleophilic agents. These derivatives can also be considered as ring-chain prototropic systems. There is also

[8] H. Decker, *J. prakt. Chem.* **47** (2), 28 (1893).
[9] H. Decker and A. Kaufmann, *J. prakt. Chem.* **84** (2), 219 (1911).
[10] W. Roser, *Ann. Chem. Liebigs* **249**, 156 (1888).
[11] W. Roser, *Ann. Chem. Liebigs* **254**, 334 (1889).
[12] A. Kaufmann and P. Strübin, *Ber. deut. chem. Ges.* **44**, 680 (1911).
[13] B. B. Dey and P. L. Kantam, *J. Indian Chem. Soc.* **11**, 835 (1934).
[14] B. B. Dey and P. L. Kantam, *J. Indian Chem. Soc.* **12**, 421 (1935).
[15] B. B. Dey and P. L. Kantam, *J. Indian Chem. Soc.* **12**, 430 (1935).
[16] E. Coufalik and F. Šantavý, *Chem. listy* **47**, 1609 (1954); *Chem. Abstr.* **48**, 3816 (1954).
[17] D. Beke and Cs. Szántay, *Ann. Chem. Liebigs* **640**, 127 (1961).

the question of whether these derivatives result from the carbinolamine by nucleophilic substitution or from the amino-aldehyde (not present in a detectable amount) by carbonyl addition reactions.[18]

Thus the following problems are unsolved: (1) Does the threefold tautomerism assumed by Gadamer really exist for heterocyclic pseudo bases and which factors determine the stability of the various forms? (2) Does ring-chain tautomerism occur in the derivatives of these bases when this is formally possible, and if not, do these derivatives possess the cyclic or open-chain structure, and by what path have they been formed?

In the following sections these questions will be discussed.

II. The Structure of Bases Obtained from Heterocyclic Quaternary Ammonium Salts

If the threefold tautomerism assumed by Gadamer really exists, then this involves the simultaneous occurrence of the two fundamental types of tautomerism.[17,19–21] The carbinolamine (**5**) and the amino-aldehyde form (**7**) form a *cationotropic* (prototropic) system because the interconversion of the two forms requires the elimination of a proton and its addition elsewhere with simultaneous rearrangement of the electronic structure of the molecule. The relation between the carbinolamine (**5**) and the quaternary ammonium hydroxide (**4**) is a type of anionotropy, as the transition of the former to the latter involves the elimination of an hydroxyl group as an anion. Rigorously (**4**) is not an isomer but a dissociated form of (**5**). In the cation produced by the dissociation, the positive charge is shared between the nitrogen and the neighboring carbon atom. Hence the cation is able to form a covalent bond with a hydroxyl group, in contrast to a quaternary ammonium ion substituted only with alkyl groups. The "threefold tautomerism" is thus represented by the formulas (**4**) to (**7**), and is simultaneously an acid–base equilibrium.[22] The fact that

[18] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," pp. 575–580. Cornell Univ. Press, Ithaca, New York, 1953.
[19] D. Beke, *Periodica Polytech.* **1**, 51 (1957); *Chem. Abstr.* **52**, 9132 (1958).
[20] D. Beke, M. B. Bárczai, and L. Töke, *Magyar Kém. Folyóirat* **64**, 125 (1958); *Chem. Abstr.* **54**, 17437 (1960).
[21] D. Beke, *Acta Chim. Acad. Sci. Hung.* **17**, 463 (1958); *Chem. Abstr.* **53**, 17163 (1959).
[22] There is a formal analogy to the diazo compounds

$$[Ar-\overset{+}{N}\equiv N]OH^- \rightleftharpoons Ar-N=N-OH \underset{BH^+}{\overset{B}{\rightleftharpoons}} Ar-N=N-O^- \underset{B}{\overset{BH^+}{\rightleftharpoons}} Ar-NH-N=O$$
$$\Big\downarrow\Big\uparrow$$
$$[Ar-N=N]_2O$$

this equilibrium can also lead to the formation of a dimolecular ether (**8**)[23,24] complicates it still further.

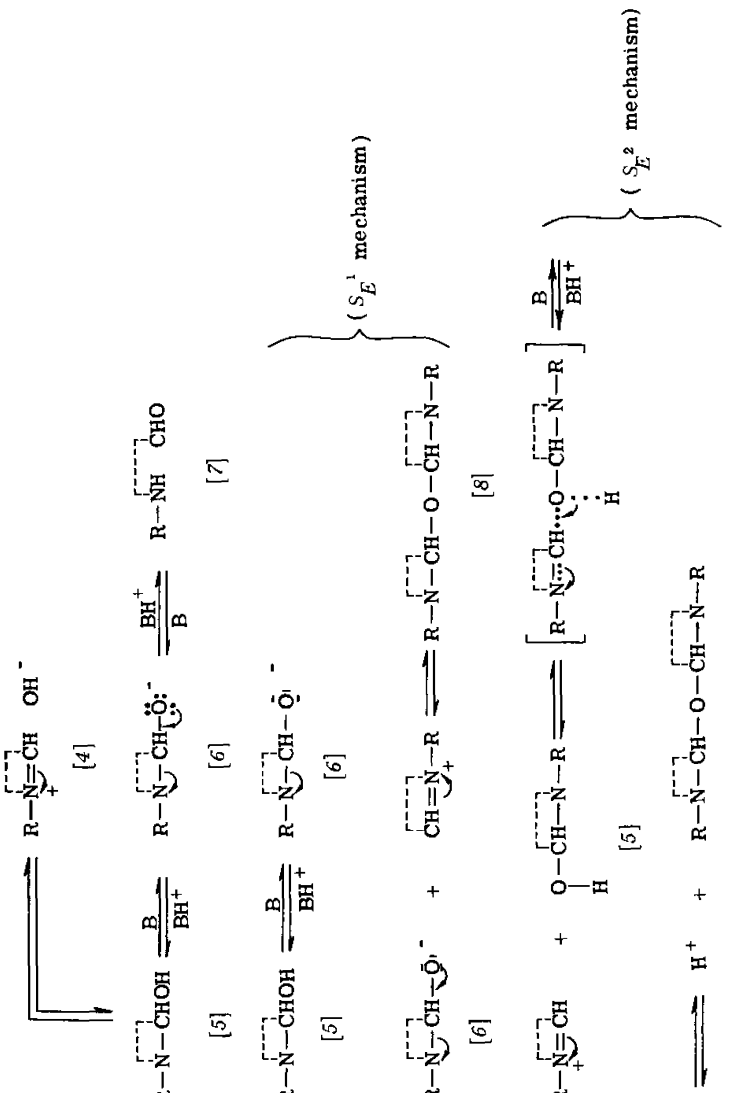
Anionotropy and prototropy are, obviously, processes that mutually oppose each other. The more polar the C—OH bond in (**5**), i.e., the more the equilibrium (**5**) $\rightleftharpoons$ (**4**) will favor (**4**) [or in other words, the stronger the base (**5**)], the less probable will be the prototropic change (**5**) $\rightarrow$ (**7**). Anionotropy and prototropy, i.e., the three tautomeric forms, could only occur simultaneously for moderately basic carbinolamines, since only these could be amphoteric.

The polarity of the C—OH bond, i.e., the basicity of the carbinolamine, depends on its structure, particularly on the stability of the ring system (degree of aromatic character), and the electron affinity of the substituents on nitrogen and carbon. Of course, external factors also play an important role in the equilibrium: temperature, polarity of the solvent, and presence or absence of catalysts (the solvent can also act as a catalyst).

Combination of the hydroxyl ion with the mesomeric cation involves the removal of a double bond. For the quaternary pyridinium compounds this causes the total loss of the aromaticity. For quaternary quinolinium and isoquinolinium compounds, the aromatic character of one of the two rings is lost, and for the quaternary acridinium compounds that of one out of three. Hence the order of stabilities of these compounds (determined by Hantzsch[2]) is explained.[18,25] Comparison of quaternary 3,4-dihydroisoquinolinium compounds and their isoquinolinium analogs with respect to the equilibrium (**5**) $\rightleftharpoons$ (**4**) shows that a much higher hydroxyl ion concentration is necessary for the isoquinolinium ions to form the carbinolamine.[26,27] This is because the transition from the quaternary 3,4-dihydroisoquinolinium ions into the undissociated carbinolamine involves significantly smaller loss of mesomeric energy than that for the quaternary isoquinolinium hydroxides.[25]

The naturally occurring bases usually contain a methyl group as a substituent on nitrogen. Methyl or other electron-repelling groups on

[23] J. G. Aston, *J. Am. Chem. Soc.* **53**, 1448 (1931).
[24] J. G. Aston and P. A. Lasselle, *J. Am. Chem. Soc.* **56**, 426 (1934).
[25] W. J. Gensler *in* "Heterocyclic Compounds," (R. C. Elderfield, ed.), Vol. IV. pp. 469–471. Wiley, New York, 1952.
[26] Ch. Tinkler, *J. Chem. Soc.* **101**, 1245 (1912).
[27] B. Skinner, *J. Chem. Soc.* p. 823 (1950).



nitrogen raise the polarity of the C—OH bond and facilitate elimination of OH as an anion. Simultaneously the strength of the C—N and O—H bonds is raised and the cyclic form is stabilized. Electron withdrawing substituents on nitrogen reduce the polarity of the C—OH bond, i.e., decrease the basicity of the compound. The C—N and O—H bonds can be weakened to such an extent that ring opening and the transfer of the proton from oxygen to nitrogen occurs.[28] Substituents on carbon can similarly influence the electron density on the carbinolamine carbon atom and, therefore, the polarity of the C—OH bond.[29]

The effect of the polarity of the solvent is obvious. Any particular carbinolamine is more dissociated in a more polar solvent than in a less polar one.

These relationships are well illustrated by a comparison of the dissociation constants of cotarnine and some analogs.[30] Changing the *N*-methyl group of cotarnine[31–35] for groups with stronger +I effect (ethyl, isopropyl) leads to analogs which are almost completely dissociated in aqueous solution at comparatively small dilutions (1:128). (Cotarnine at the same dilution is 74% dissociated.) The degree of dissociation of cotarnine analogs with *N*-benzyl or *N*-aryl groups decreases with increasing electron affinity of the substituent. Stepwise removal of the alkoxyl groups from the aromatic ring causes significant decreases in the dissociation. If the nitrogen atom carries a strong electron withdrawing group (e.g., 2,4-dinitrophenyl), then only the open-chain amino-aldehyde form is stable.[36]

Even in the most recent literature, erroneous views still appear repeatedly. Therefore, it is necessary to emphasize that the chemical reactions can be used to decide questions of tautomerism only in exceptional cases. The investigations of Baeyer and Oekonomides[37,38] on isatin showed that the principle of least alteration in structure is certainly not generally valid and that the structure of a reactant cannot always be deduced from the structure of a reaction product. Already in 1897, Wislicenus[39] had emphasized that chemical reactions, in general, and acylation and alkylation, in particular, cannot be used to prove the structure of compounds subject to rearrangement.

For a mobile equilibrium, provided sufficient time is available for the mutual transformation between the two isomers, both forms can produce derivatives that could only be derived from one of them. This holds even if the reactive form is present in very small concentration; because of the constant reattainment of equilibrium the whole mass will finally react. However, if a reaction that could be given only by one particular form does not occur, the absence of this isomer at least is demonstrated.

Recently, Nesmeyanov and co-workers[40] have published definitive evidence that *dual reactivity* (the formation of derivatives of two different structural formulas) extends beyond *tautomerism* (isomers in equilibrium or reversible isomeric transformation). A single molecular species can form two series of derivatives, in one of which a transfer of the reaction center occurs in the reaction.

In the case of the bases derived from quaternary heterocyclic ammonium salts, the carbinolamines **(5)** can react as cyclic aldehyde-ammonias with many reagents with which the amino-aldehyde **(7)** could react. However, reactions of the carbinolamines which are not characteristic of amino-aldehydes are also known. Carbinolamines can easily be reconverted into the quaternary salts by the action of dilute acids, and they form alkyl ethers very easily with alcohols. If these last reactions do not occur, then this is convincing evidence for the base possessing the amino-aldehyde structure. However, if these reactions do occur this does not provide unambiguous confirmation of the carbinolamine structure. They are also given by the bimolecular ethers **(8)**, and, in the case of a tautomeric equilibrium

[28] Th. Zincke, *Ann. Chem. Liebigs* **330**, 361 (1904).
[29] M. I. Kabachnik and A. I. Zitser, *Zhur. Obshchei Khim.* **7**, 162 (1937); *Chem. Abstr.* **31**, 4320 (1937).
[30] D. Beke, Cs. Szántay, and L. Töke, *Periodica Polytech.* **3**, 177 (1959).
[31] D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.* **13**, 377 (1958); *Chem. Abstr.* **52**, 14616 (1958).
[32] D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.* **16**, 439 (1958); *Chem. Abstr.* **53**, 5267 (1959).
[33] D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.* **19**, 259 (1959); *Chem. Abstr.* **54**, 2387 (1960).
[34] D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.* **19**, 267 (1959); *Chem. Abstr.* **54**, 2388 (1960).
[35] D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.* **20**, 407 (1959); *Chem. Abstr.* **54**, 8819 (1960).
[36] D. Beke, Cs. Szántay, M. Bárczai-Beke, *Acta Chim. Acad. Sci. Hung.* **21**, 153 (1959).

[37] A. v. Baeyer and S. Oekonomides, *Ber. deut. chem. Ges.* **15**, 2093 (1882).
[38] A. v. Baeyer and S. Oekonomides, *Ber. deut. chem. Ges.* **16**, 2193 (1883).
[39] W. Wislicenus, *Samml. chem. und chem.-tech. Vorträge* **2**, 187 (1897).
[40] A. N. Nesmeyanov and M. I. Kabachnik, *Zhur. Obshchei Khim.* **25**, 41 (1955); *Chem. Abstr.* **50**, 1577 (1956).

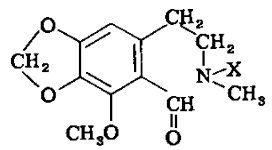
(5) ⇌ (7), such a reaction can involve the whole of the substance present even though the amino-aldehyde greatly predominates in the equilibrium mixture. Equally, the acylation and alkylation with the formation of various derivatives with an open-chain structure is no evidence for the amino-aldehyde structure. However, if such reactions do not occur this shows unambiguously that the compound (for example, alkaloid berberine) does not contain a secondary amino group and, thus, it cannot be considered as an amino-aldehyde. In special cases comparative kinetic investigations of selected chemical reactions with the help of suitable model compounds can be used for the clarification of the true structure of the bases.

A simple method of distinguishing the carbinolamines (**5**), the bimolecular ethers (**8**), and the amino-aldehydes (**7**) from one another depends on their different behavior toward the Karl-Fischer reagent.[41] The carbinolamines and their bimolecular ethers can be directly titrated against the Karl-Fischer reagent where they each react with an amount of reagent equivalent to one molecule of water, i.e., the ethers with half as much reagent per hetero ring as the corresponding carbinolamines. The amino-aldehydes do not react at all under these conditions (in the presence of much pyridine) with the Karl-Fischer reagent. Obviously this method cannot be used where the amino-aldehyde can easily isomerize to the carbinolamine under the experimental conditions.

These structural problems are also insoluble by physical methods alone. The infrared spectrum often gives an unambiguous decision about the structure in the solid state: the characteristic bands of the carbonyl or the hydroxyl group decided whether the compound in question is a carbinolamine or an amino-aldehyde. However, tautomeric equilibria occur only in solution or in the liquid or gaseous states. Neither infrared nor ultraviolet spectroscopy are sufficiently sensitive to investigate equilibria in which the concentration of one of the isomers is very small but is still not negligible with respect to the chemical reaction.

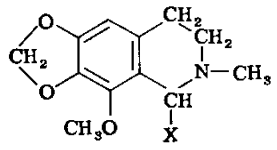
From the foregoing considerations it follows that the problems of threefold tautomerism postulated by Gadamer can only be solved by the simultaneous use of various physical and chemical methods. This is well demonstrated by using cotarnine as an example.

The aqueous solution of cotarnine reacts strongly alkaline. According to the foregoing discussion this points to the greater stability of the cyclic form. Infrared spectra indicate crystalline cotarnine to be in the carbinolamine form (**2**): the characteristic absorption maximum of an aldehyde conjugated with an aromatic ring is absent. Such carbonyl bands are found in the spectrum of *N*-methylcotarnine (**9a**) and *N*-acetylcotarnine (**9b**) at 1685 and 1680 cm^{-1}, respectively. However, cotarnine shows a band at 3100 cm^{-1}, characteristic of strongly associated OH group.[21,42,43]



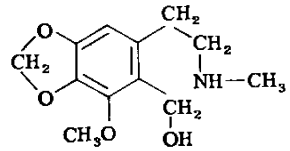
[*9*]

[*9a*] : X = CH_3
[*9b*] : X = $COCH_3$
[*9c*] : X = COC_6H_5



[*10*]

[*10a*] : X = H
[*10b*] : X = OC_2H_5
[*10c*] : X = CN



[*11*]

According to Dobbie *et al.*,[44] the ultraviolet spectrum of cotarnine in dilute aqueous or alcoholic solution is identical with that of cotarnine chloride [(**1**), Cl^- instead of OH^-], but in nonpolar solvents it is identical with that of hydrocotarnine (**10a**), 1-ethoxy-hydrocotarnine (**10b**), and cotarnine pseudocyanide (**10c**). This is in agreement with Decker's[45] view of the structure of cotarnine and with the conclusions of Hantzsch and Kalb.[2] Measurement of electrical conductivity in-

[41] D. Beke, Cs. Szántay, and M. Bárczai-Beke, *Periodica Polytech.* **4**, 329 (1960).

[42] D. Beke, D. Korbonits, and R. Kornis-Markovits, *Ann. Chem. Liebigs* **626**, 225 (1959).
[43] W. Schneider and B. Müller, *Ann. Chem. Liebigs* **615**, 34 (1958).
[44] J. J. Dobbie, A. Lauder, and Ch. Tinkler, *J. Chem. Soc.* **83**, 598 (1903).
[45] H. Decker, *Ber. deut. chem. Ges.* **33**, 2273 (1900).

dicated[2] that cotarnine exists, depending on the conditions, either as the carbinolamine (**2**) or as the quaternary ammonium hydroxide (**1**) derived from this by dissociation, or in a mobile equilibrium mixture of both these forms. Dobbie *et al.*[46] reproduced the spectra of cotarnine solutions containing varying amounts of potassium hydroxide by using cotarnine chloride and hydrocotarnine and by dissolving mixtures of the latter two compounds or by placing the separate solutions of these compounds in the apparatus in series. Thus no evidence could be obtained for the occurrence of the amino-aldehyde (**3**) postulated by Roser.[10,11] Steiner,[47] Kitasato,[48] and Skinner[27] came to similar conclusions. The band at 285 mμ in alkaline solutions is not due to an aromatic aldehyde.[49] This band also occurs in the spectrum of hydrocotarnine (**10a**)[50,51] and in the carbinolamine (**11**)[52] which contain no aldehyde group. This is a "B band,"[53] which occurs in the spectra of all aromatic compounds.

The R band characteristic for aromatic aldehyde groups[53] (aldehyde $n \rightarrow \pi$ bands)[54] occurs in the spectrum of *N*-methylcotarnine (**9a**) and that of *N*-benzoylcotarnine (**9c**), which are real aldehydes, at 330 mμ in the form of an inflection. Even in alkaline solution the hypothetical amino-aldehyde form of cotarnine can only occur in amounts not detectable by spectroscopic methods.

Comparative polarographic investigations[55,56] show a significant difference in the polarographic behavior of cotarnine and that of *N*-methylcotarnine. The polarographically active form of cotarnine is the cotarninium ion, even in strongly alkaline solution.

[46] J. J. Dobbie, A. Lauder, and Ch. Tinkler, *J. Chem. Soc.* **85**, 121 (1905).
[47] P. Steiner, *Bull. soc. chim. biol.* **6**, 231 (1924); *Chem. Zentr.* p. 1559 (2), (1924).
[48] Z. Kitasato, *Acta Phytochim. (Japan)* **3**, 247 (1927); *Chem. Zentr.* p. 1965 (2), (1927).
[49] L. Láng, M. Bárczai-Beke, and D. Beke, *Magyar Kém. Folyóirat* **67**, 364 (1961); *Periodica Polytech.* **5**, 313 (1961).
[50] K. Folkers and F. Koniuszy, *J. Am. Chem. Soc.* **62**, 1673 (1940).
[51] K. Folkers, F. Koniuszy, and J. Shavel, Jr., *J. Am. Chem. Soc.* **64**, 2146 (1942).
[52] Cs. Szántay, L. Szeghy, and D. Beke, *Magyar Kém. Folyóirat* **68**, 240 (1962). *Periodica Polytech.* **6**, 113 (1962).
[53] E. A. Braude, *Ann. Repts. Progr. Chem. (Chem. Soc. London)* **42**, 105 (1945).
[54] M. Pestemer and D. Brück *in* "Methoden der organischen Chemie (Houben-Weyl, ed.), Vol. III/2, p. 673. Georg Thieme Verlag, Stuttgart, Germany, 1955.
[55] K. Györbiró, *Periodica Polytech.* **3**, 267 (1959).
[56] K. Györbiró, *Periodica Polytech.* **4**, 61 (1960).

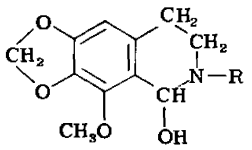
The determination of the degree of dissociation of cotarnine[30] and the good agreement with the values derived from measurements of electrical conductivity with those from the spectrophotometric methods is indirect evidence that no significant part of the undissociated cotarnine is in the amino-aldehyde form. In the conductance calculation, the undissociated part was neglected. If this included a significant amount of amino-aldehyde (i.e., a secondary base), there would be a noticeable discrepancy in the degree of dissociation obtained by the two methods.

Kinetic investigation of the reaction of cotarnine and a few aromatic aldehydes (*N*-methylcotarnine, *m*-nitrobenzaldehyde) with hydrogen cyanide[57] in anhydrous tetrahydrofuran showed such differences in the kinetic and thermodynamic parameters for cotarnine compared to those for the aldehydes, and also in the effect of catalysts, so that the possibility that cotarnine was reacting in the hypothetical amino-aldehyde form could be completely eliminated. Even if the amino-aldehyde form is present in concentrations under the limit of spectroscopic detection, then it still certainly plays no part in the chemical reactions. This is also expected by Kabachnik's[58] conclusions for the reactions of tautomeric systems where the equilibrium is very predominantly on one side.

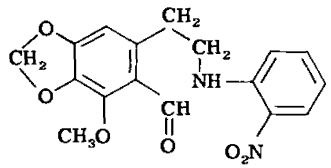
Thus, for cotarnine, it is impossible with the available evidence to decide whether this is a tautomeric equilibrium in which one form is very predominant or no ring-chain tautomerism occurs. For the first-mentioned alternative, it should be possible to shift the complicated acid–base equilibria by structural alteration of the cotarnine molecule so that all the equilibrium forms become detectable. As already mentioned, the introduction of aryl groups in place of the cotarnine *N*-methyl group leads, in parallel with increasing electron affinity of the aryl group, to bases with continually decreasing degrees of dissociation,[30] until finally, with strongly electron attracting aryl groups, the carbinolamine form only exists momentarily as it is formed from the quaternary salt and then spontaneously changes into the open-chain amino-aldehyde.[36] According to the infrared spectrum, *N*-phenylnorcotarnine,[31] *N*-(*p*-chlorophenyl)norcotarnine,[33]

[57] D. Beke, Cs. Szántay, and M. Bárczai-Beke, *Ann. Chem. Liebigs* **636**, 150 (1960).
[58] M. I. Kabachnik *in* "Problemi Mechanizma Organichesskich Reakcii," p. 126. Academy of Sciences of the Ukranian SSSR, Kiev, 1954.

as well as *N*-(*p*-nitrophenyl)norcotarnine[59] have carbinolamine structures in the crystalline state (**12a–c**); *N*-(*o*-Nitrophenyl)norcotarnine[59] is, however, an amino-aldehyde (**13**). In the 6,7-dimethoxy series the *N*-(*p*-nitrophenyl) derivative is already in the amino-aldehyde form (**14**).

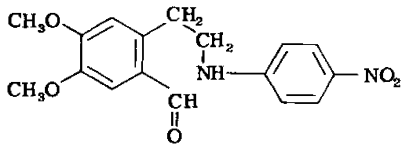


[*12*]



[*13*]

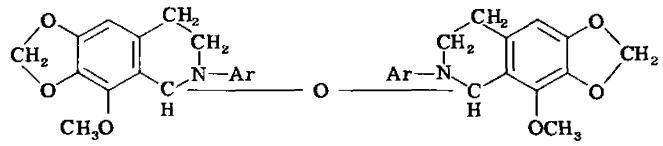
[*12a*]: R = phenyl
[*12b*]: R = *p*-chlorophenyl
[*12c*]: R = *p*-nitrophenyl



[*14*]

On the basis of the dissociation constant values, it seems sensible to conclude that, in these moderately basic carbinolamines, the hydrogen atom of the hydroxyl group is sufficiently acid to be eliminated under the influence of an alkali and by its transfer to the nitrogen atom of the mesomeric anion, the formation of the amino-aldehyde form may result. Instead of the amino-aldehyde, however, the corresponding bimolecular ether (**15a–c**) can be obtained.[60] It can be concluded that the formation of the bimolecular ether (S_E1 or S_E2 mechanism) and the formation of the amino-aldehyde (B-S_E1 or B-S_E2' mechanism) are competitive reactions. It seems probable that where the first reaction can occur the latter one is pushed into the background. The triple tautomeric system postulated by Gadamer

[59] D. Beke and E. Eckhart, *Magyar. Kém. Folyóirat* in press; *Chem. Ber.* **95**, 1059 (1962).
[60] D. Beke and co-workers, unpublished work (1960).

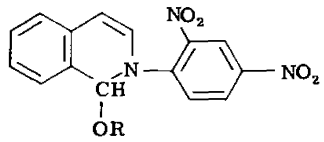


[*15*]

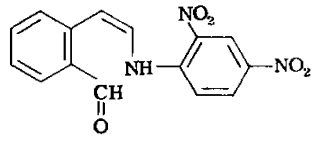
[*15a*]: Ar = phenyl
[*15b*]: Ar = *p*-chlorophenyl
[*15c*]: Ar = *p*-nitrophenyl

thus does not necessarily occur even if the simultaneous occurrence of anionotropy and prototropy is possible.

Following the 3,4-dihydroisoquinolinium compounds, the isoquinolinium compounds themselves will now be considered. The violet red compound obtained by Zincke[61] by heating 1-hydroxy-2-(2,4-dinitrophenyl)-1,2-dihydroisoquinoline (**16a**) is the open-chain amino-aldehyde (**17**) isomeric with (**16a**)[17] and is not the hemiacetal (**18**) as assumed by Zincke. This is the first case in which both the members

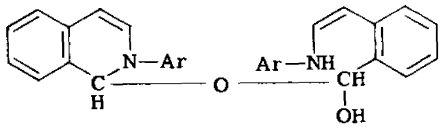


[*16*]



[*17*]

[*16a*]: R = H
[*16b*]: R = *n*-C_4H_9



[*18*]

Ar = 2, 4 - dinitrophenyl

of a pseudo-base ring-chain prototropic system has been isolated or even that their existence has been demonstrated. However, the quater-

[61] Th. Zincke, *Ann. Chem. Liebigs* **396**, 103 (1913).

nary ammonium hydroxide form is not known and also bimolecular ether formation was not observed. Investigations of reaction kinetics have shown that **(16)** and **(17)** are interconvertible.[17] Thus, in suitable conditions, dynamic equilibrium, i.e., true tautomerism, occurs between the two compounds.[62]

Thus among the known pseudo bases derived from heterocyclic quaternary ammonium salts, the following principal types can be differentiated according to their basicity:

a. Strong bases which occur in the carbinolamine form in the solid state and in the nonpolar solvents but which completely or partly dissociate into the mesomeric cation and hydroxide ions[63] in polar solvents. The amino-aldehyde form cannot be detected using either physical or chemical methods.

b. Moderately strong bases which occur as carbinolamines in the solid state. In aqueous solution they are in equilibrium with their ions and also with their bimolecular ethers and change spontaneously to the latter even in nonpolar solvents. The amino-aldehyde form has not yet been detected in this class.

c. Carbinolamines which do not dissociate into cations and hydroxide ions. These can be converted into the isomeric amino-aldehydes, and both forms can be isolated or detected and occur simultaneously in suitable conditions in a dynamic equilibrium.

d. Compounds which do not show pseudo basic properties at all (insoluble in dilute aqueous acids). These occur only in the amino-aldehyde form; the carbinolamine form is formed transiently on basification of the quaternary salt.

The great majority of the compounds investigated belong to types a and b, i.e., they occur in the carbinolamine form. The possibility that the triple tautomerism postulated by Gadamer exists cannot, therefore, be completely eliminated, but its existence has not been demonstrated in one single case. In complete contrast to the usual view, it certainly cannot be considered as a general or frequent

[62] A. Müller and co-workers [*Ber. deut. Chem. Ges.* **76**, 855 (1943); *Ber. deut. chem. Ges.* **75**, 891 (1942); *Acta Chim. Acad. Sci. Hung.*, in press] observed similar behavior with some isobenzopyrylium salts. If warmed in aqueous solution they are transformed into isobenzopyranols and these change on warming in ethyl acetate into the isomeric diketones by ring opening.

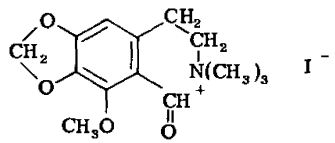
[63] F. Kröhnke [*Ann. Chem. Liebigs* **600**, 211 (1956)] assumes that *N*-(2,6-dichlorobenzyl)quinolinium hydroxide is also completely dissociated in ions.

phenomenon. At most it could only occur as an exception by a fortuituous coincidence of structural factors and experimental conditions.

III. Structure and Mechanism of Formation of Derivatives of the Heterocyclic Pseudobasic Carbinolamines

The heterocyclic pseudobasic carbinolamines show a very varied reactivity. However, the structure of a large number of their transformation products, in particular those from which conclusions have been drawn as to the structure of the initial pseudo base, are incorrect even in the most recent literature.

Those derivatives that result by the action of acylating and alkylating reagents, such as *N*-acetylcotarnine **(9b)**, *N*-benzoylcotarnine **(9c)**, or "cotarnmethin methyliodide" **(19)** can only be derived from



[19]

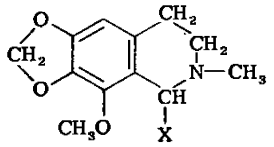
the amino-aldehyde form of whatever structure the initial base possessed.

By contrast, derivatives formed by the action of certain nucleophilic reagents (e.g., H_2O_2, alcohols, mercaptans, CN^-, SO_3H^-,[64] Grignard compounds) can only exist in a cyclic form. The most that can occur here is an equilibrium between the nondissociated and the dissociated form (for example, pseudocyanide and true cyanide),[2] if the newly formed C—O, C—S, or C—C bond is sufficiently polar.

The reaction products formed by other nucleophilic reagents (e.g., amino compounds or carbanions derived from carbonyl or nitro compounds) can be considered as ring chain prototropic systems. The newly formed C—N or C—C bond in the cyclic form of these compounds is more or less polar (evidence for this is the sensitivity to

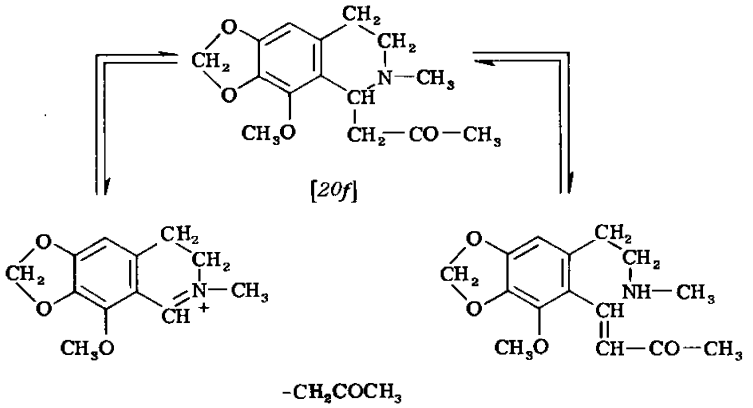
[64] D. Beke and M. Bárczai-Martos, *Acta Chim. Acad. Sci. Hung.* **11**, 295 (1957); *Chem. Zentr.* p. 11575 (1957).

acids and the easy mutual exchange of substituents[31-34,64-73]), and, thus, it is also necessary here to consider the possibility of dissociation in polar solvents, i.e., Gadamer's view of a triple tautomerism of the bases can formally also be applied to these derivatives (for example, "anhydrocotarnine acetone"):



[20]

[20a] : X = NHC_6H_5 [20e]: X = CH_2COOH
[20b] : X = NHOH [20f]: X = CH_2COCH_3
[20c] : X = $NHNHC_6H_5$ [20g]: X = CH_2NO_2
[20d] : X = $NHCONH_2$ [20h]: X = $CH_2COC_6H_5$

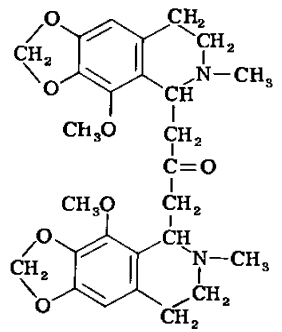


$-CH_2COCH_3$

[65] D. Beke and K. Harsányi, *Acta Chim. Acad. Sci. Hung.* **11**, 303 (1957).
[66] D. Beke, K. Harsányi, and J. Körösi, *Acta Chim. Acad. Sci. Hung.* **11**, 309 (1957); *Chem. Zentr.* p. 9784, (1958).
[67] D. Beke and K. Harsányi *Acta Chim. Acad. Sci. Hung.* **11**, 349 (1957); *Chem. Abstr.* **52**, 5437 (1958).
[68] F. Kröhnke and K. Ellegast, *Ann. Chem. Liebigs* **600**, 176 (1956).
[69] F. Kröhnke and K. Ellegast *Ann. Chem. Liebigs* **600**, 198 (1956).
[70] F. Kröhnke and I. Vogt, *Ann. Chem. Liebigs* **600**, 211 (1956).
[71] F. Kröhnke and I. Vogt, *Ann. Chem. Liebigs* **600**, 228 (1956).
[72] F. Kröhnke and H. L. Honig, *Chem. Ber.* **90**, 2215 (1957).
[73] F. Kröhnke and I. Vogt, *Chem. Ber.* **90**, 2227 (1957).

Ingold[18] makes no differentiation in principle between pseudo bases and those derivatives which are formed by the action of nucleophilic reagents. The latter he denotes by the general term "pseudo salts" and considers their formation parallel to the formation of the carbinolamines themselves. If the mesomeric cation combines with a hydroxide ion, a pseudo base is formed; if it combines with another nucleophilic ion or molecule, then a pseudo salt is formed.

Ultraviolet and infrared spectroscopic investigations and also chemical behavior show unambiguously that the compounds which result from the last-mentioned type of nucleophilic reagent and cotarnine possess the cyclic form.[65-67] Examples of these are "cotarnine anil" (**20a**), "cotarnine oxime" (**20b**), "cotarnine phenylhydrazone" (**20c**), "anhydrocotarnine carbamide" (**20d**), "hydrocotarnylacetic acid" (**20e**), "anhydrocotarnine acetone" (**20f**), and also the compound (**21**) obtained from two molecules of cotarnine and one molecule of acetone by the elimination of two molecules of water. The cyclic form had ben demonstrated earlier for "anhydrocotarnine-nitromethane" (**20g**) and "anhydrocotarnine-acetophenone" (**20h**).[75,76]

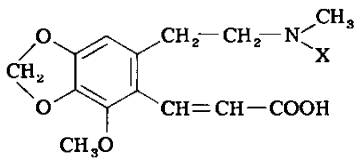


[21]

In spite of this, even in the most recent literature such derivatives have been considered to be derived from the amino-aldehyde

[74] V. Grignard and co-workers, "Traité de chimie organique," Vol. 20, p. 545. Masson, Paris, 1953.
[75] E. Hope and R. Robinson, *J. Chem. Soc.* **99**, 2114 (1911).
[76] E. Hope and R. Robinson, *J. Chem. Soc.* **103**, 361 (1913).

form.[74,77-79] However, the cyclic structure of "hydrocotarnine acetic acid" (**20e**) and the two condensation products of cotarnine with acetone (**20f, 21**) were even unambiguously determined by chemical methods alone.[66,67] These compounds were not reduced either catalytically nor by sodium amalgam, although "acetylhydrocotarnine acetic acid" (**22b**) is easily reduced by both these methods. If even a small pro-



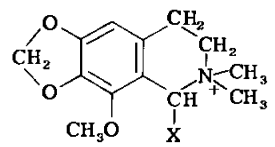
[*22*]

[*22a*]: X = H
[*22b*]: X = CH_3CO

portion of hydrocotarnine acetic acid existed in the open-chain olefinic form (**22a**), then this would absorb hydrogen, and, because of the continual re-establishment of the equilibrium, the whole would eventually be converted into the open-chain saturated derivative. Although bromine adds smoothly to (**22b**), it causes substitution in the 5-position for (**20e**), (**20f**), and (**21**). Ultraviolet and infrared evidence is also available for the cyclic structure.

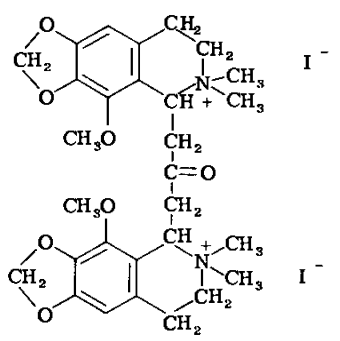
However, these authentic cyclic compounds are converted by acetic anhydride or methyl iodide into derivatives of the hypothetical aminoaldehyde form. Methylation gives first the cyclic methiodides (**23a–b**) and (**24**) which occur by the addition of a single molecule of methyl iodide; in the presence of sodium hydroxide and excess methyl iodide these are converted into the open-chain quaternary methiodides (**25a–b**) and (**26**). Similar examples have been given by Gardent[80] and by Gensler and co-workers.[81-83]

[77] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV/A, pp. 598,- 664. Elsevier, Amsterdam, 1957.
[78] F. Klages, "Lehrbuch der organischen Chemie," Vol. III, p. 558. Walter de Gruyter, Berlin, 1958.
[79] P. Karrer, "Lehrbuch der organischen Chemie," 13th ed., p. 930. G. Thieme, Stuttgart, Germany, 1959.
[80] J. Gardent, *Bull. soc. chim. France* p. 1260 (1957).
[81] W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.* **73**, 5555 (1951).

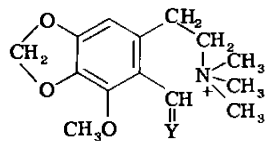


[*23*]

[*23a*]: X = CH_2COOH
[*23b*]: X = CH_2COCH_3

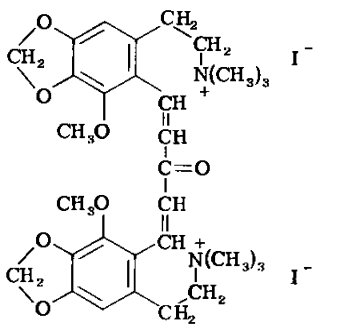


[*24*]



[*25*]

[*25a*]: Y = CHCOOH
[*25b*]: Y = $CHCOCH_3$

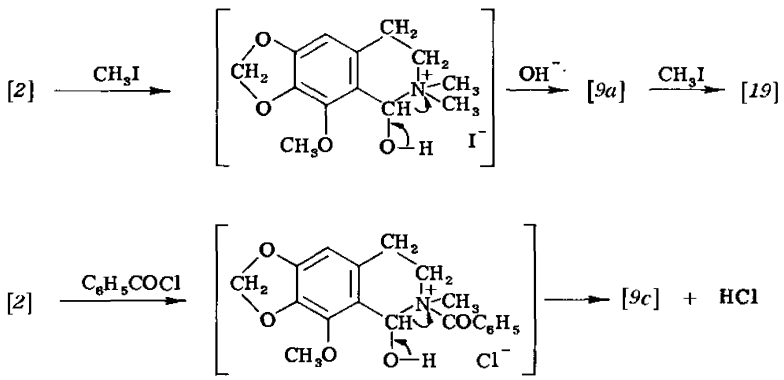


[*26*]

Obviously, such a nucleophilic elimination reaction with ring opening (exhaustive methylation) should be even easier in the case of cotarnine and other analogous carbinolamines because there the proton is removed from an oxygen atom instead of a carbon atom. Electrophilic alkylation and acylating reagents attack on the nucleophilic nitrogen atom of a carbinolamine, and open-chain derivatives can be formed via cyclic intermediates or transition states. The formation of both cyclic derivatives and those which formally belong

[82] W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.* **74**, 2959 (1952).
[83] W. J. Gensler, E. M. Healy, J. Onshuus, and A. L. Bluhm, *J. Am. Chem. Soc.* **78**, 1713 (1958).

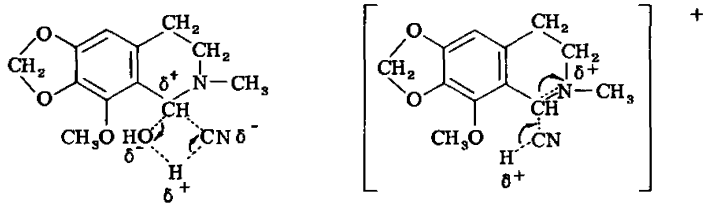
to the ring-chain prototropic system can thus be considered to occur from the carbinolamine or from the amino-aldehyde (see Scheme 1).



Scheme 1

Thus cotarnine pseudocyanide, which is certainly cyclic, can formally be derived from the carbinolamine (or the dissociated form) by exchange of anions or from the amino-aldehyde by the addition of hydrogen cyanide followed by elimination of water and ring closure. As already mentioned, the kinetics of the reactions of cotarnine and several aromatic aldehydes with hydrogen cyanide[57] definitely eliminate the latter possibility. The reaction of cotarnine with hydrogen cyanide occurs in anhydrous tetrahydrofuran, a solvent of low polarity in which the cotarnine is not dissociated to a measurable extent so that it exists only as the carbinolamine and possibly the hypothetical amino-aldehyde. The reaction here is fast and, quantitatively, second order, and also strongly accelerated by catalytic amounts of acetic acid. The reactions of *N*-methylcotarnine (structurally analogous to amino-aldehyde form of cotarnine) and also that of *m*-nitrobenaldehyde by contrast are slow equilibrium reactions, characterized by general base catalysis and not influenced by acetic acid. In the reaction of cotarnine with hydrogen cyanide, the HCN molecule probably reacts with the oxygen atom of the hydroxyl group which is itself linked to the strongest nucleophilic center of the cotarnine molecule; the transition state is represented by (**27**). The presence of

acetic acid turns yellow the originally colorless tetrahydrofuran solution of cotarnine, indicating the formation of cotarninium ions. Obviously, these react more quickly with the strongly polar hydrogen cyanide; here the transition state is represented by (**28**).



[27] [28]

It is concluded that in the formation of the other pseudo salts and in the mutual interconversions of pseudo salts, it is similarly the cyclic form which reacts.

This assumption is supported *inter alia* by the kinetics of the formation of the butyl ether (**16b**) from the amino-aldehyde (**17**).[17] The kinetic and thermodynamic parameters show conclusively that during the reaction the amino-aldehyde first changes into the isomeric carbinolamine (**16a**) and that the latter reacts with *n*-butanol to form the ether.

A generally applicable reaction scheme naturally cannot be given. The reaction mechanism of one particular carbinolamine with a particular reagent can depend on the reaction conditions; in nonpolar solvents, the nondissociated carbinolamine obviously reacts (S_N2 mechanism). In polar solvents, on the other hand, the mesomeric cation reacts (S_N1 mechanism). Formally all these reactions belong to the general class of "aminomethylation."[84,85] The reaction products can be considered to be "Mannich bases."

As an over-all conclusion, it can be stated that the assumption of ring-chain tautomerism in the pseudo bases derived from the heterocyclic quaternary ammonium salts is quite unnecessary as an explanation of the formation of two (cyclic and open-chain) types of deriva-

[84] H. Hellmann and G. Opitz, *Angew. Chem.* **68**, 265 (1956).
[85] H. Hellmann, G. Aichinger, and H. P. Wiedemann, *Ann. Chem. Liebigs* **626**, 35 (1959).

tives. Nucleophilic reagents react at the electrophilic carbinol carbon atom with the formation of cyclic derivatives, whereas the attack of electrophilic acylating and alkylating reagents necessarily occurs at the nucleophilic nitrogen atom with resulting formation of open-chain products.

Aza Analogs of Pyrimidine and Purine Bases of Nucleic Acids

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I. Introduction

Nucleic acids have recently attracted the attention of very numerous laboratories. This is because nucleic acids belong to the most important components of living matter, for genetic traits are fixed in them and transmitted through them. Nucleic acids also play the main role during biosynthesis of specific proteins.

As is well-known, nucleic acids consist of a polymeric chain of monotonously reiterating molecules of phosphoric acid and a sugar. In ribonucleic acid, the sugar component is represented by D-ribose, in deoxyribonucleic acid by D-2-deoxyribose. To this chain pyrimidine and purine derivatives are bound at the sugar moieties, these derivatives being conventionally, even if inaccurately, termed as pyrimidine and purine bases. The bases in question are uracil (in ribonucleic acids) or thymine (in deoxyribonucleic acids), cytosine, adenine, guanine, in some cases 5-methylcytosine and 5-hydroxymethylcytosine. In addition to these, a number of the so-called odd bases occurring in small amounts in some ribonucleic acid fractions have been isolated.

In view of the fact that the principal chain is formed by regularly alternating residues of phosphoric acid and sugar, it follows that the structural variety and the diversity of life functions related to it must be based on the sequence and on the kind of bases of nucleic

acids. This sequence, in which the bases are bound to the principal chain is now generally accepted as a code according to which biological information is "recorded" in a nucleic acid molecule. This fact obviously directs the attention to more detailed investigation of nucleic acid bases.

One of the lines of approach of such an investigation is the study of analogs of nucleic acid bases. The objective here is to prepare such analogs as would be incorporated into the nucleic acid molecules on the basis of their similarity to the natural species or as could interfere at some of the steps of nucleic acid biosynthesis.

If the incorporation of the analogs results in a changed property of the nucleic acid formed, it is possible to study in this way the role of nucleic acids in living systems. With the analogs of nucleic acid bases which interfere with one of the biosynthetic reactions of nucleic acids, the possibility of selective action and, thus, also of chemotherapeutical application is envisaged. Similar attention is given to other nucleic acid components, i.e., to the nucleosides (ribosyl or deoxyribosyl derivatives of the bases) and to nucleotides (nucleoside phosphates). Here there is also the possibility of altering the sugar moiety. These substances, too, can be employed in one of the ways mentioned. It should be added at this point, however, that not every analog can be considered as an antimetabolite without any further examination; the antimetabolite character of an analog must be established by studying its interactions in biological systems.

The possibility of interfering with the structure or formation of nucleic acids with the aid of such antimetabolites obviously has great practical significance. An interference with growth of neoplastic tissue and influence on the genetic properties of an organism should be mentioned in the first place.

The analogs of pyrimidine and purine bases can be derived by purely formal structural modifications or, more rationally, from the results of biochemical investigation.

An important group of antimetabolites are the aza analogs of pyrimidine and purine bases which are theoretically derived by a replacement of the methine group of a pyrimidine or purine nucleus with a nitrogen atom. This replacement represents a relatively minor alteration of the structure of these substances as it does not change the functional groups, practically preserves the molecular weight, and produces almost isosteric compounds. The replacement of the methine

group with a nitrogen atom can be effected in position 5 or 6 of the pyrimidine base. This results in analogs described as "5-aza" and "6-aza." With the purine bases the replacement can take place either in position 2 or 8, this leading to 2- and 8-aza analogs, respectively.

The formal derivation of the analogs, described in the foregoing, represents, from the point of view of systematic organic chemistry, a shift to the derivatives of other heterocyclic systems. In the case of pyrimidine aza analogs we are dealing with derivatives of symmetrical or asymmetrical triazine; in the case of purine aza analogs, the derivatives produced are those of imidazo[4,5]-*v*-triazine and *v*-triazolo[4,5-*d*]pyrimidine.

For this reason dual terminology is in use for the aza analogs. The first, derived from the principal pyrimidine and purine derivatives by means of the prefix "aza-" is used almost exclusively in biochemical papers; in organic chemistry is it used (together with the systematic names) wherever it is desired to compare the properties of the natural bases and of their aza analogs. The systematic terminology is naturally used in the older literature where no biochemical aspects of the compounds were considered, and in some newer work of strictly chemical nature. Since the numbering of the substituents is in some cases different for the different systems, we shall discuss this in more detail later.[1]

The chemistry of the aza analogs of pyrimidine bases represents a part of the chemistry of the corresponding heterocyclic (triazine) group and frequently has been developed from earlier work with different objects. In keeping with its title, the present review occupies itself with those substances which were recently tested as aza analogs and further with substances which could be considered as such. Together with these, some other compounds are treated that are related to their preparation and closer study. This results in including some of the near derivatives of the aza analogs proper.

Main attention is devoted to recent papers, mostly of the last decade. In the interest of presenting a unified view of the problem,

[1] It should be stated that the nomenclature of the triazine derivatives is not uniform, e.g., in *Chemical Abstracts* the compounds are often indexed according to another system than that used in the original papers, and an additional system could have been used for this review. To avoid further complications, the author will use the commonest nomeclature in accordance with the representative monographs in this field (see references 12 and 45.)

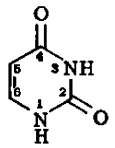
some of the older work is mentioned in passing. Since even a brief review of the studies concerning the biological activity of these substances would exceed the scope of this article, no biochemical papers are included.

II. Aza Analogs of Pyrimidine Bases

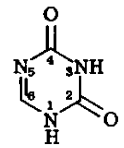
A. 5-Aza Analogs

1. *Nomenclature*

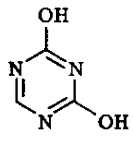
The names of these compounds as aza analogs were coined in the same way as those of the 6-aza analogs employing the frequently used numbering of uracil (**1**). This nomenclature is most often used for the principal aza analogs of pyrimidine bases (e.g., 5-azauracil); it is rarely used for further systematic derivatives.



[*1*]



[*2*]



[*3*]

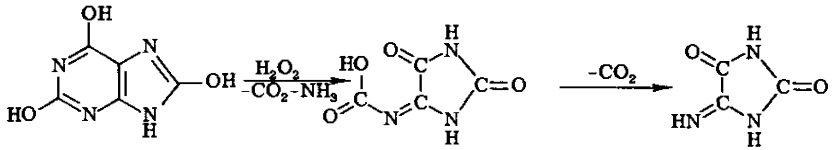
According to the triazine nomenclature, 5-azauracil is 2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazine (**2**). The subject index of *Chemical Abstracts* prefers "s-triazine-2,4(1*H*,3*H*)-dione." Furthermore, some authors use a name derived from the lactim structure, 2,4-dihydroxy-*s*-triazine (**3**). The numbering of the substituents is the same for all these types of nomenclature.

2. *2,4-Dioxo-1,2,3,4-tetrahydro-1,3,5-triazine (5-Azauracil)*

a. Methods of Preparation. The chemistry of the 5-aza analogs of the pyrimidine bases forms a relatively isolated group in the very extensive field of derivatives of *s*-triazine. It developed practically independently of the other substances of this series.

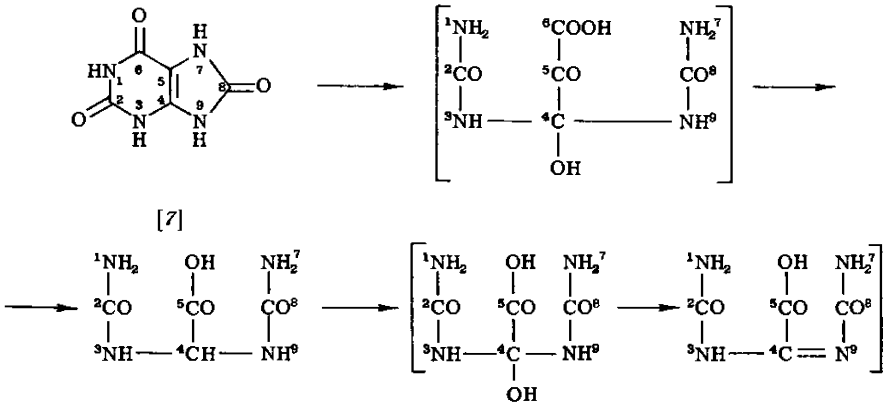
Brandenberger[1a-3] showed in 1954 that the structure of 2,4-dioxo-1,2,3,4-tetrahydro-*s*-triazine (**2**) is that of allantoxaidine which had been heretofore formulated as iminohydantoin (**6**) on the basis of a suggestion of Ponomarev[4] and subsequent work of Biltz and Robl.[5,6]

Allantoxaidine is formed by decarboxylation of oxonic (allantoxanic) acid (**5**) which is the product of alkaline oxidation of uric acid (**4**) with hydrogen peroxide. This reaction was studied in detail by several authors[7-9] and was expressed as follows:



[*4*] [*5*] [*6*]

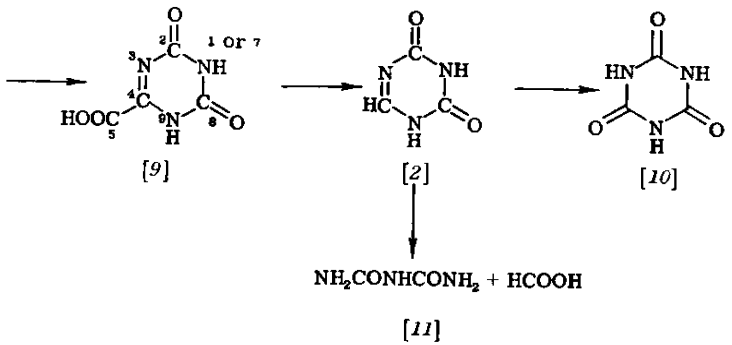
Brandenberger[1a-3] and later, independently, Canellakis and Cohen,[10] and Hartman and Fellig[11] studied the course of the oxidation with uric acid specifically labeled with C^{14}. On the basis of their work they formulated the course of the oxidation as shown in Scheme **1**.



[*7*]

[*8*]

[1a] H. Brandenberger, *Helv. Chim. Acta* **37**, 641 (1954).
[2] H. Brandenberger and R. Brandenberger, *Helv. Chim. Acta* **37**, 2207 (1954).
[3] H. Brandenberger, *Experientia* **12**, 208 (1956).
[4] J. Ponomarev, *Ber. deut. chem. Ges.* **11**, 2156 (1878).
[5] H. Biltz and R. Robl, *Ber. deut. chem. Ges.* **53**, 1967 (1920).
[6] H. Biltz and R. Robl, *Ber. deut. chem. Ges.* **54**, 2441 (1921).
[7] C. S. Venable, *J. Am. Chem. Soc.* **40**, 1099 (1918).
[8] F. J. Moore and R. M. Thomas, *J. Am. Chem. Soc.* **40**, 1120 (1918).
[9] H. Biltz and A. Schauder, *J. prakt. Chem.* **106**, 108 (1923).
[10] E. S. Canellakis and P. P. Cohen, *J. Biol. Chem.* **213**, 379 (1955).
[11] S. Hartman and J. Fellig, *J. Am. Chem. Soc.* **77**, 1051 (1955).



SCHEME 1

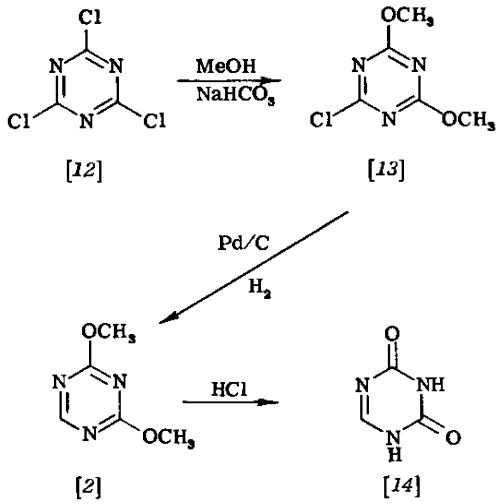
Its oxidation to cyanuric acid (**10**) and its hydrolysis to biuret (**11**) and formic acid[4,5] is also in agreement with the new formulation of allantoxaidine as a triazine derivative. A very strained explanation[6] would be required to make these reactions conform to the original structure.

All these findings, as well as the similarity of UV spectra[2,11] caused dioxotetrahydrotriazine to be classified as the simplest member of the formerly known 6-substituted derivatives. These derivatives are not interesting in connection with the analogs of natural pyrimidine bases and have been reviewed elsewhere.[12] The structure of allantoxaidine and its appurtenance to the triazine series have been recently demonstrated by its unequivocal synthesis.

Flament *et al.*[13] made use of the partial replacement of two chlorine atoms in cyanuric chloride (**12**) with methoxyl groups, the 2,4-dimethoxy-6-chloro-1,3,5-triazine (**13**) formed was dehalogenated to 2,4-dimethoxy-1,3,5-triazine (**14**) and this yielded the product (**2**) on gentle hydrolysis.

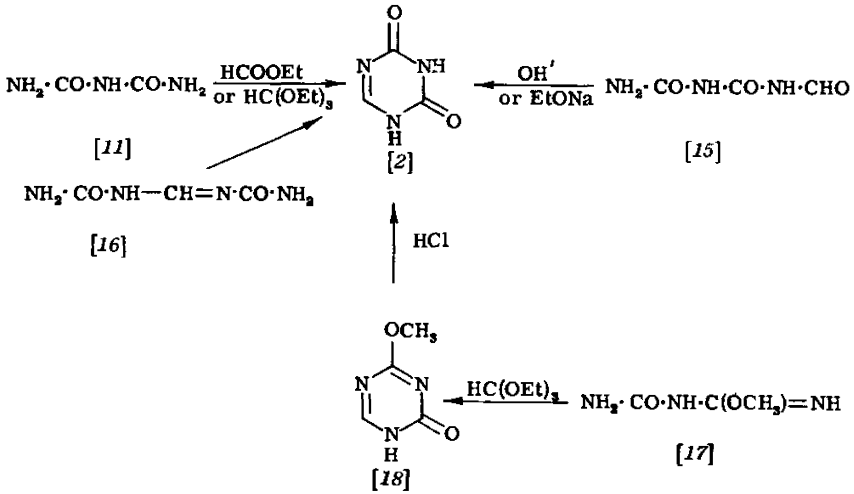
The common method of preparation of 6-alkyl-2,4-dioxotetrahydrotriazines is the cyclization of acyl-biurets by aqueous hydroxide.[12] Formyl biuret which should by analogy yield 5-azauracil had not been known until recently. Its transient formation can be expected during further synthesis of 5-azauracil. Píškala and Gut[14] achieved

[12] E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Vol. 13 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 202. Interscience, New York, 1959.
[13] I. Flament, R. Promel, and R. H. Martin, *Helv. Chim. Acta* **42**, 485 (1959).
[14] A. Píškala and J. Gut, *Collection Czechoslov. Chem. Communs.* **26**, 2519 (1961).



the cyclization of biuret (**11**) with ethyl formate in the presence of sodium ethylate. The view that formyl biuret (**15**) might be an intermediate product of these reactions was later confirmed by the cyclization[15] of the recently described formyl biuret[16] under the influence of alkalies. For further synthesis of 5-azauracil, the cyclization of *N,N'*-dicarbamylformamide (**16**) by sodium ethoxide[14] was used. The yields of both the last-named syntheses are about 60%. Runti[17] and co-workers cyclized biuret by orthoformate in the presence of sulfuric acid. The yield of the reaction was not published. It is even more convenient and productive to cyclize *O*-methylisobiuret (**17**) with ethyl orthoformate. The 4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (**18**) formed is readily converted to 5-azauracil.[18] The possibility of hydrolysis of 5-azauracil in an alkaline medium during the syntheses described requires thoroughly anhydrous conditions.[14] This is apparently the cause of the unsuccessful attempt at cyclization of biuret with ethyl formate.[13] A recent preliminary note reports a simple but not unambiguous synthesis of 5-azauracil consisting of heating urea with trisformaminomethane or ethyl orthoformate.[18a]

[15] H. Eilingsfeld, M. Seefelder, and A. Weidinger, *Angew. Chem.* **72**, 836 (1960).
[16] Badische Anilin- & Soda-Fabrik, A. G.; German Auslegeschrift 1110625 (1961).
[17] C. Runti, L. Sindellari, and F. Ulian, *Ann. chim. (Rome)* **50**, 847 (1960).
[18] A. Píškala and J. Gut, *Collection Czechoslov. Chem. Communs.*, in press.
[18a] H. Bredereck, F. Effenberger, and A. Hofmann, *Angew. Chem.* **74**, 354 (1962).



b. Properties. According to an investigation of the IR spectra,[19] the results of which are generally identical with the spectra of uracil and 6-azauracil (e.g., Section II,B,2,b), 5-azauracil possesses the dilactam structure. The UV spectra[19] of 5-azauracil and of its *N*-alkyl and *O*-alkyl derivatives display, contrary to our expectation, only minor differences. For this reason no final conclusions can be drawn as to the tautomeric equilibrium of 5-azauracil in aqueous solutions. A similar situation was observed for the analogous compounds[20] and appears to be characteristic for these systems.

A determination of the dissociation constants[14,21,22] of the compounds reveals that 5-azauracil ($pK_a = 6.73$) is practically of the same acidity as 6-azauracil and considerably more acidic than uracil.

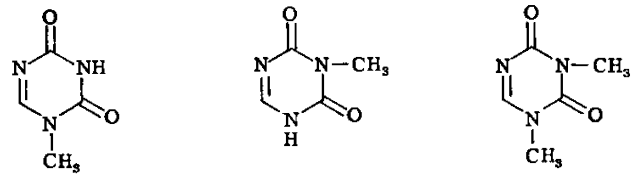
A fundamental difference between 5-azauracil, on the one hand, and 6-azauracil and uracil, on the other, lies in the low stability of 5-azauracil toward acid and especially to alkaline hydrolysis.[4] This fact appears to be in agreement with the differences in electron densities of these substances computed by the simple MO-LCAO method.[23]

[19] M. Horák, J. Jonáš, A. Pískala, and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 2754 (1962).
[20] S. F. Mason, *in* "Ciba Foundation Symposium on the Chemistry and Biology of Purines" (G. E. W. Wolstenholme and C. M. O'Connor, eds.). J. and A. Churchill, London, 1957.
[21] J. Jonáš and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 716 (1962).
[22] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).
[23] R. Zahradník, J. Koutecký, J. Jonáš, and J. Gut, *Collection Czechoslov. Chem. Communs.*, in press.

3. *N-Alkyl Derivatives of 5-Azauracil*

The study of the *N*-alkyl derivatives of allantoxaidine was taken up by Biltz who proceeded from its formerly accepted hydantoin structure and obtained its monomethyl[24] and dimethyl[25] derivatives.

Final structure determination of the monomethyl derivatives was made possible only on performing straightforward syntheses of the compounds, analogous to syntheses of allantoxaidine. The 1-methyl (**19**) and 3-methyl (**20**) derivatives were prepared by cyclization of 1- and 3-methyl biuret,[14] respectively. The 3-methyl derivative was also obtained by cyclization of *N,N'*-bis(methylcarbamyl)formamidine.[14] The 1-methyl derivative was the same as the product obtained by Biltz[24] on methylation of silver salt of allantoxaidine with methyl iodide. The same product is formed primarily during methylation of dioxotriazine with diazomethane.[14] An excess of this agent produces the expected 1,3-dimethyl derivative[25] (**21**). These results of alkyl-



[19] [20] [21]

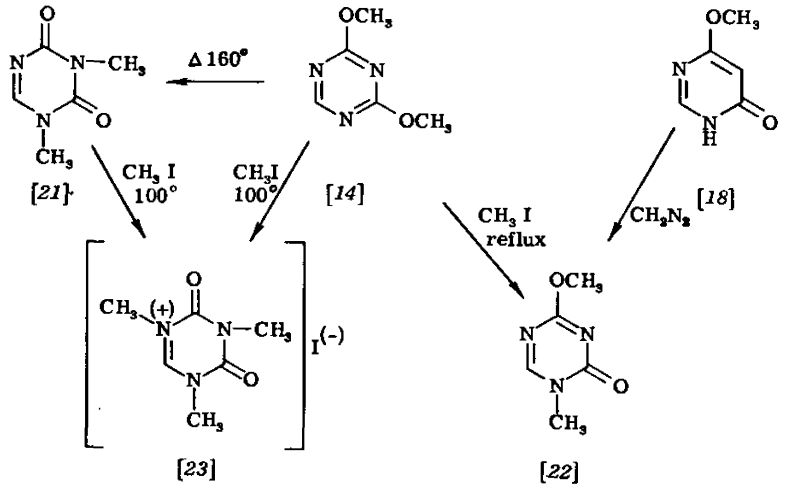
ation are in agreement with the study of the dissociation constants of 5-azauracil and of both of its *N*-methyl derivatives (1-methyl derivative $pK_a = 8.15$; 3-methyl derivative $pK_a = 6.58$). On the assumption that the effect of the methyl group is negligible, the pK_a values permit the conclusion to be drawn that the dissociation sets in first at the N-1 atom.[14,21] In this respect the behavior of 5-azauracil is identical with that of uracil but contrary to that of 6-azauracil (e.g., Section II,B,3,a).

By a more detailed study of the reaction of 5-azauracil with diazomethane[25a] it was found that this reaction is considerably accelerated by the presence of a small amount of water, methanol, or dimethylformamide. It does not proceed appreciably in absolute ether. By

[24] H. Biltz and H. Hanisch, *J. prakt. Chem.* [2] **112**, 138 (1926).
[25] H. Biltz and R. Robl, *Ber. deut. chem. Ges.* **54**, 2448 (1921).
[25a] A. Pískala, *Collection Czechoslov. Chem. Communs.*, in press.

chromatographic separation of mixtures obtained on using excess diazomethane and the catalytic influence of the foregoing substances, it was possible to isolate small amounts of the 1-methyl-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (**22**), in addition to the main product, the 1,3-dimethyl derivative. On adding 15% dimethylformamide, a small amount of 2,4-dimethoxy-1,3,5-triazine (**14**) was also obtained. These results demonstrate the very different behavior of 5-azauracil as compared with uracil and 6-azauracil where no formation of *O*-methyl derivatives could be observed.

The pyrimidine compounds are known to undergo a rearrangement of the *O*-alkyl derivatives to the *N*-alkyl ones.[26] The methoxy derivatives of 1,3,5-triazine display a similar behavior. On applying methyl iodide to 2,4-dimethoxy-1,3,5-triazine one of the methyl groups is shifted giving rise to 1-methyl-4-methoxy-derivative (**22**). This compound was also obtained by methylation of 4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (**18**) with diazomethane. At higher temperature (100°C) in presence of methyl iodide a shift of both methyl groups takes place and methiodide is formed simultaneously (**23**). Similarly,



on heating 2,4-dimethoxy-1,3,5-triazine alone both methyl groups are shifted. The reactions of the methoxy derivatives of 1,3,5-triazine are

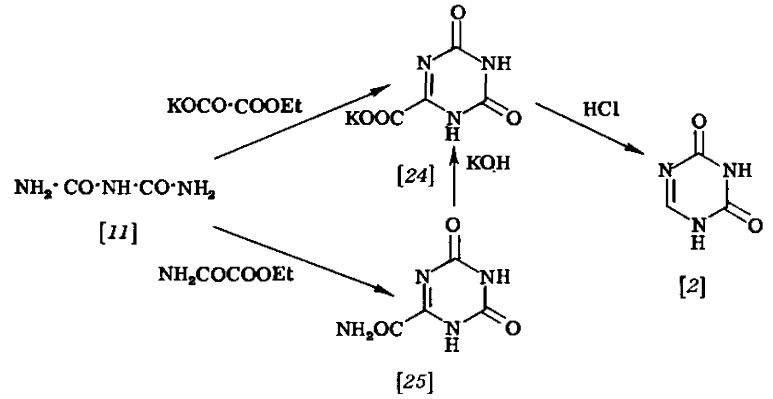
[26] G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 2001 (1930).

thus analogous to those of the analogous pyrimidine derivatives but they proceed with some difficulty and especially the thermal rearrangement gives rise to further products as yet unidentified. The formation of a methiodide is also at variance with the pyrimidine compounds, an analogous reaction being impossible with the latter.[26a]

A similar rearrangement accompanied by decarboxylation was described for 2,4-dimethoxy-1,3,5-triazine-6-carboxylic acid.[27]

4. *2,4-Dioxo-1,2,3,4-tetrahydro-1,3,5-triazine-6-carboxylic Acid (5-Azaorotic Acid)*

The name 5-azaorotic acid should be given to allantoxanic (oxonic) acid but it is not yet commonly used. The elucidation of the correct structure of this compound was closely linked to the solution of the course of oxidation of uric acid mentioned earlier.

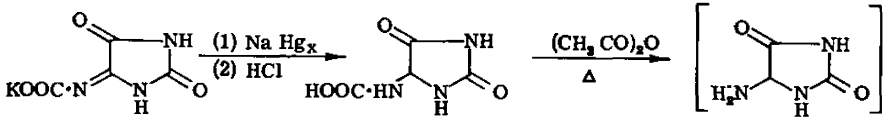


The structure (**5**) originally proposed by Ponomarev[4] appeared to be confirmed by the conversion of dihydrooxonic acid to allantoin performed by Biltz and Giesler.[28] Biltz and Robl[5] showed later that oxonic acid is identical with allantoxanic acid obtained on oxidation of allantoin.[29] Since that time both these trivial names are in usage.

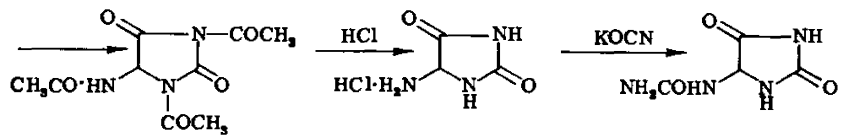
[26a] A. Piskala and J. Gut, *Collection Czechoslov. Chem. Communs.*, in press.
[27] E. Kober, *J. Org. Chem.* **26**, 5259 (1961).
[28] H. Biltz and E. Giesler, *Ber. deut. chem. Ges.* **46**, 3410 (1913).
[29] E. Mulder, *Ann. Chem. Liebigs* **159**, 365 (1871).

Works on the oxidation of uric acid has unequivocally established the triazine structure[1-3,10,11] (9) of oxonic acid. This is further confirmed by the straightforward synthesis described by Pískala and Gut.[30] The reaction of biuret (11) with potassium ethyloxalate yielded a potassium salt (24), that with ethyl oxamate, the amide of oxonic acid (25). Both these compounds were converted to 5-azauracil. An analogous reaction with diethyloxalate which should produce an ester of oxonic acid resulted in a mixture of urethane and parabanic acid, however.

The same authors[30] elucidated the origin of allantoin from hydroxonic acid[28] on which the original hydantoin structure (5) was based and which was formulated as shown in Scheme 2.



[5] [26] [27]

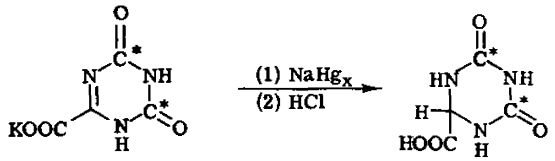


[28] [29] [30]

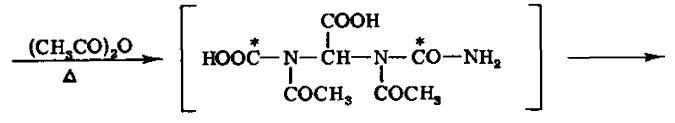
SCHEME 2

For studying this reaction, oxonic acid prepared by the aforementioned synthetic procedure from biuret-(2,4-C^{14}) was used; it was converted to hydroxonic acid (31) by reduction with sodium amalgam. According to the formulation of Biltz and Giesler,[28] nonradioactive carbon dioxide would be expected from its reaction with acetanhydride. Since, however, one-half of the activity of the starting substance was present in the escaping carbon dioxide, it must be assumed that the ring is cleaved and the reaction is as shown in Scheme 3.

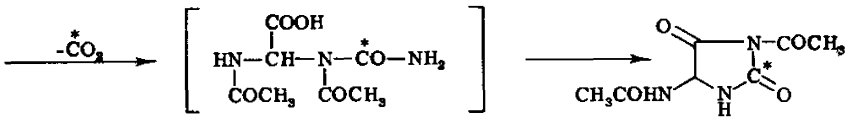
[30] A. Pískala and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 1562 (1962).



[9] [31]



[32]



[33] [28]

SCHEME 3

Hence, by this pathway the formation of allantoin is not at variance with the triazine structure of oxonic acid.

5. *2,4-Dioxohexahydro-1,3,5-triazine and Its Derivatives*

The 6-alkyl derivatives of 2,4-dioxohexahydro-1,3,5-triazine have been known for some time and have been reviewed earlier.[31]

The unsubstituted member of this series (34) was prepared only later, by cyclization of methylenebisurea.[32,33]

Attempts to prepare this substance by reduction of dioxotetrahydro-1,3,5-triazine with sodium amalgam,[24] hydroiodic acid, or tin in acetic acid,[28] were accompanied by hydrolytic cleavage of the ring. Only

[31] E. M. Smolin and L. Rapoport, "s-Triazines and Derivatives," Vol. 13 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 210. Interscience, New York, 1959.

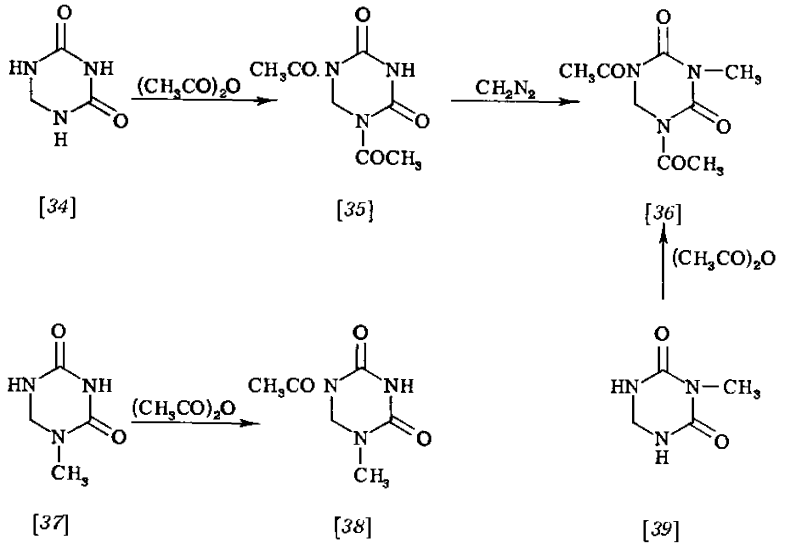
[32] O. Diels and R. Lichte, *Ber. deut. chem. Ges.* **59**, 2778 (1926).

[33] F. B. Slezak, A. Hirsch, L. J. Krimen, and H. A. McElravy, *J. Org. Chem.* **25**, 1672 (1960).

when the mixture was maintained acid during reduction with sodium amalgam[11] was it possible to prepare the desired hexahydro derivative.

Hydrogenation with Adams' catalyst took place only with the 6-alkyl derivatives.[34] Dioxohexahydrotriazine itself acted as a catalyst poison (in common with 1,3,5-triazine and cyanuric acid[35]). Dioxotetrahydrotriazine as well as its *N*-alkyl and 6-alkyl derivatives can be readily hydrogenated by using Raney nickel.[14]

The hexahydro derivatives are weakly basic substances, some of them forming hydrochlorides.[31] Dioxohexahydrotriazine yields a 1,5-diacetyl derivative (**35**), in which the positions of the acetyl groups were determined by acetylation of the *N*-alkyl derivatives and methylation with diazomethane according to Scheme 4.[30]



[34] [35] [36] [37] [38] [39]

SCHEME 4

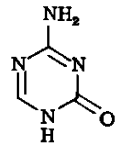
The course of acetylation here is analogous to that of dioxohexahydro-1,2,4-triazine (e.g., Section II,B,8).

6. *4-Amino-2-oxo-1,2-dihydro-1,3,5-triazine (5-Azacytosine)*

The 5-aza analog of cytosine could be taken as 4-amino-2-oxo-1,2-dihydro-1,3,5-triazine (**40**) which was prepared by the reaction of

[34] A. Ostrogovich and G. Ostrogovich, *Gazz. chim. ital.* **26**, 48 (1936).
[30] H. Brandenberger and R. Schwyzer, *Helv. Chim. Acta* **38**, 1396 (1955).

dicyandiamide and 100% formic acid.[36] The structure of this compound was recently confirmed by an unambiguous synthesis[18] from



[40]

the methoxyderivative (**18**). The chemistry of the related 6-substituted derivatives has been studied extensively[37] but it is of no interest in the present connection.

7. *Other Related Derivatives*

Other derivatives of *s*-triazine, in particular the 2,4-disubstituted ones, are usually prepared by total synthesis and are therefore not closely linked with the chemistry of 5-azauracil unlike the analogous derivatives of 1,2,4-triazine. 2,4-Dimethoxy-1,3,5-triazine was mentioned earlier (e.g., Section II,A,2,a), the other substances are not related to the present subject.

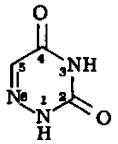
B. 6-Aza Analogs

1. *Nomenclature*

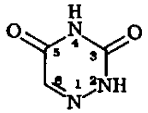
Names describing these substances as aza analogs of pyrimidine bases are generally derived from the more common type of numbering of uracil (**1**). According to this system the methine group in position 6 is replaced (**41**). The nomenclature of other derivatives is based on this principle quite systematically and is in general use. The numbering of the position of substituents by this method is the same as in the analogous pyrimidine derivatives. This is of special advantage in comparing the derivatives of 6-azauracil (especially nucleosides and nucleotides) with similar derivatives of uracil. In such cases it will also be used in this chapter.

[36] C. Grundmann, L. Schwennicke, and E. Beyer, *Chem. Ber.* **87**, 19 (1954).
[37] E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Vol. 13 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 189. Interscience, New York, 1959.

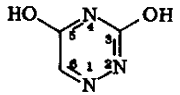
According to systematic triazine nomenclature, 6-azauracil is 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (**42**). The indexes of the *Chemical Abstracts* describe it as *as*-triazine-3,5(2*H*,4*H*)-dione. In addition



[*41*]



[*42*]



[*43*]

to this the literature contains nomenclature derived from the dilactim form (**43**), 3,5-dihydroxy-1,2,4-triazine.

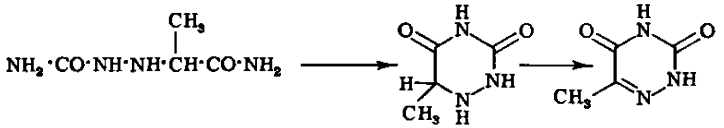
In all types of nomenclature based on triazine the numbering of the substituents is shifted by one as compared with the nomenclature of 6-aza analogs of pyrimidines.

2. *3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazines (6-Azauracil and Its 5-Alkyl Derivatives)*

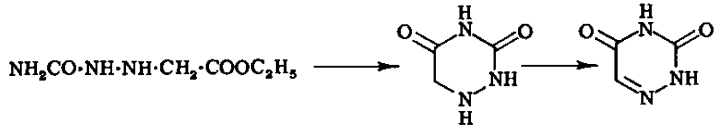
The chemistry of the 6-aza analogs of pyrimidine bases which has been developed from the biochemical aspect since about 1956 was based on work reported in relatively numerous older papers. In spite of the fact that 6-azauracil was prepared only in 1947 and suitable syntheses were described only quite recently, substances of this type and methods of their preparation had been known for a long time. The chemistry of 6-aza analogs of pyrimidine bases is therefore relatively closely linked with the chemistry of the 1,2,4-triazine derivatives.

a. Methods of Preparation. The first method of preparation of substances of this type (**45**) was described by Thiele and Bailey[38] who cyclized the amide of α-semicarbazidopropionic acid (**44**) prepared from acetaldehyde semicarbazone. Later on a similar cyclization of ethyl semicarbazidoacetate[39] (**47**) was employed to prepare dioxohexahydrotriazine (**48**). This method was later used for the preparation of the hexahydro derivatives of this type as will be seen later (e.g., Section II,B,8).

[38] J. Thiele and J. Bailey, *Ann. Chem. Liebigs* **303**, 75 (1898).
[39] J. R. Bailey and W. T. Read, *J. Am. Chem. Soc.* **36**, 1764 (1914).



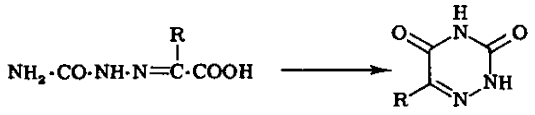
[*44*] [*45*] [*46*]



[*47*] [*48*] [*42*]

In this connection the possibility of oxidation of these substances to the tetrahydro derivatives should be mentioned. It was made use of by Thiele and Bailey[38] for the preparation of 6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (6-azathymine) (**46**) and only recently by Grundman *et al.*[40] for that of 6-azauracil (**42**).

Of greater importance for the preparation of these substances is the reaction first observed by Locquin[41] in 1906 and independently treated later by Bougault.[42,43] These authors have shown that semicarbazones of α-keto acids (**49**) are cyclized under the influence of aqueous sodium hydroxide directly to the 6-substituted 2,5-dioxotetrahydro-1,2,4-triazines (**50**). The reaction was usually carried out at



[*49*] [*50*]

100°C; higher yields are obtained by working at room temperature but the reaction takes several months.[44] The cyclization proceeds best

[40] C. Grundmann, H. Schroeder, and R. Rätz, *J. Org. Chem.* **23**, 1522 (1958).
[41] R. Locquin, *Bull. soc. chim. France* [3] **35**, 964 (1906).
[42] J. Bougault, *Compt. rend. acad. sci.* **159**, 83, 631 (1914).
[43] J. Bougault, *Ann. chim. (Paris)* [9] **5**, 317 (1916).
[44] E. Cattelain, *Bull. soc. chim. France* **9**, 907 (1942).

with semicarbazones with a higher alkyl or even better an aryl or aralkyl group in the α-position. For this reason the reaction was used first of all for the preparation of numerous 6-aryl and 6-aralkyl derivatives as reviewed by Erickson *et al.*[45] Some other substances[46] of this type were prepared later by a similar method.

With semicarbazones of lower α-keto acids the reaction proceeds with some difficulty or not at all. Thus, the semicarbazones of pyruvic acid[42,43,47] cannot be cyclized and that of glyoxylic acid[48] is predominantly hydrolyzed so that the yield of the cyclization product is only 20–25%.[40] This reaction was used in work with a different object, for preparing 6-azauracil,[48] for the first time.

For unsubstituted or lower alkylated dioxotriazines, it is advantageous to cyclize semicarbazones by sodium ethylate in ethylene glycol as described by Chang and Ulbricht.[49] In this reaction 6-azauracil is obtained in 66% yield. The procedure was used for the preparation of labeled 6-azauracil[49] and later for the synthesis of a number of 6-alkyl derivatives including 6-azathymine.[50]

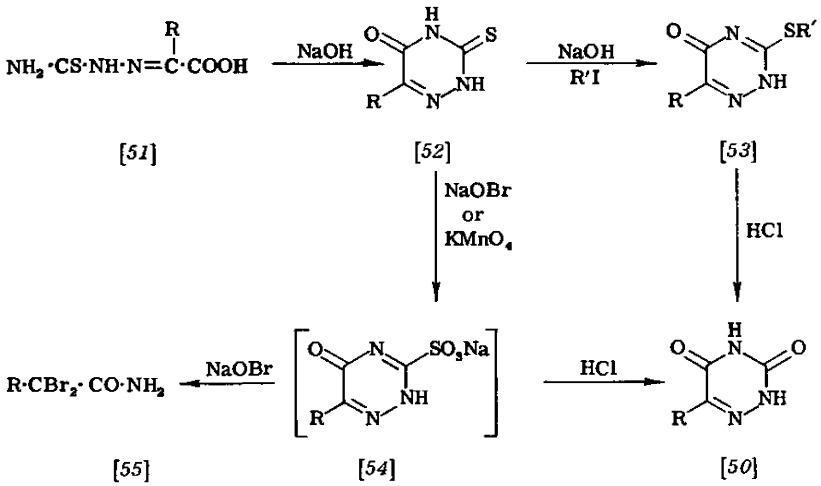
The starting semicarbazones were most often prepared directly from the α-keto acids. Godfrin[51] proceeded from α-alkyl acetoacetates, which were converted by oxidation with nitrosylsulfuric acid to α-keto-acid oximes and the latter transformed to semicarbazones or thiosemicarbazones by applying semicarbazide or thiosemicarbazide. For glyoxylic acid semicarbazone a very convenient procedure was employed, making use of the hydrolysis of nonisolated chloral semicarbazone.[49]

In continuing their previous work Bougault and Daniel[52,53] observed that thiosemicarbazones of α-keto acids (**51**) also undergo a cyclization resulting in 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (**52**). In contrast with the cyclization of semicarbazones this cyclization

[45] J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," Vol. 10 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 69. Interscience, New York, 1956.
[46] S. Rossi, *Gazz. chim. ital.* **83**, 133 (1953).
[47] J. R. Bailey, *Am. Chem. J.* **28**, 386 (1902).
[48] W. Seibert, *Chem. Ber.* **80**, 494 (1947).
[49] P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.* **80**, 976 (1958).
[50] P. K. Chang, *J. Org. Chem.* **23**, 1951 (1958).
[51] A. Godfrin, *J. pharm. chim.* **30**, 321 (1939); *Chem. Abstr.* **34**, 5087 (1940).
[52] J. Bougault and L. Daniel, *Compt. rend. acad. sci.* **186**, 151 (1928).
[53] J. Bougault and L. Daniel, *Compt. rend. acad. sci.* **186**, 1216 (1928).

proceeds with substantially higher yields. This reaction will be taken up in more detail later (e.g., Section II,B,4,a).

In this connection it is important to mention the finding that the thioxo derivatives (**52**) can be converted in several ways to the 3,5-dioxo derivatives. By alkylation with methyl iodide in alkaline solution, methylmercapto derivatives (**53**) are produced which are readily hydrolyzed to dioxo derivatives.[54] A similar course is followed in the reaction with ethyl chloroacetate.[55] Finally, oxidation with hypo-



bromite in an alkaline medium yields salts of the corresponding sulfonic acid (**54**) which are hydrolytically cleaved in an acid solution. However, excess hypobromite results in cleavage of the ring giving rise to α-dibromoamides[56] (**55**).

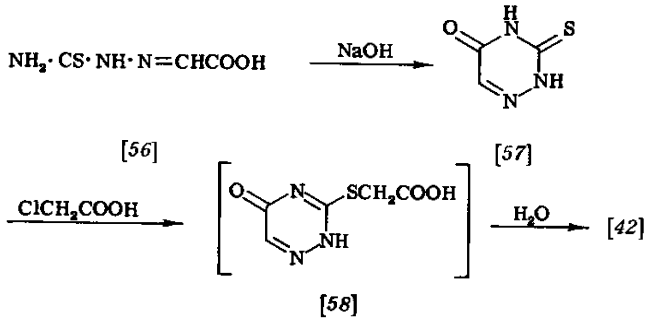
The cyclization of thiosemicarbazones has therefore recently served as the basis for further syntheses of 6-azauracil and 6-azathymine. Barlow and Welch[57] proceeded from thiosemicarbazone of mesoxalic acid (**51**, **52**; R = COOH). The corresponding methylmercapto derivative (**53**; R = COOH, R′ = CH_3) was hydrolyzed and decarboxylated

[54] E. Cattelain, *Bull. soc. chim. France* **11**, 256 (1944).
[55] E. Cattelain and P. Chabrier, *Bull. soc. chim. France* p. 700 (1948).
[56] E. Cattelain, *Bull. soc. chim. France* **12**, 47 (1945).
[57] R. B. Barlow and A. D. Welch, *J. Am. Chem. Soc.* **78**, 1258 (1956).

to yield 6-azauracil. Falco *et al.*[58] used a similar procedure starting from the diester of mesoxalic acid. The replacement of sulfur with oxygen was achieved, however, by oxidation with potassium permanganate via the corresponding sulfonic acid (**54**; R = COOH) and by subsequent hydrolysis and decarboxylation.

Oxidation with potassium permanganate was also used for the preparation of derivatives with a $CH_3(CH_2)_n$ ($n = 2,4,6,8,12$) and β-substituted vinyl[59a] group in the 6-position from the corresponding thioxo derivatives.[59]

In a further synthesis, Gut[60] used the cyclization of the thiosemicarbazone of glyoxylic acid (**56**); the 2-thioxo-5-oxo-2,3,4,6-tetrahydro-1,2,4-triazine (**57**) formed was converted to 6-azauracil by applying aqueous solution of chloroacetic acid. (This reaction will be discussed later, e.g., Section II,B,4,b.) The same procedure was used

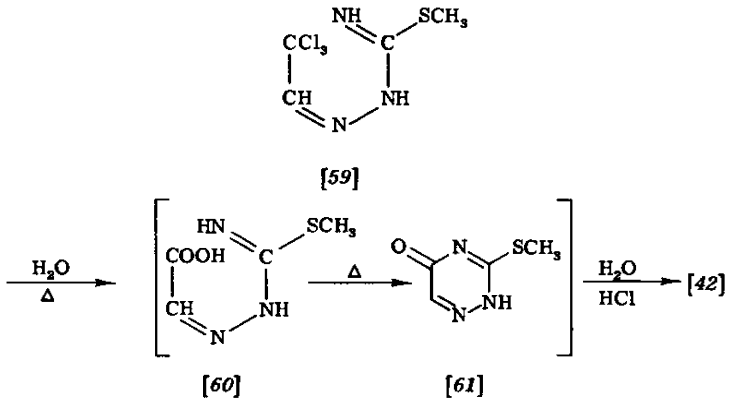


for the preparation of 6-azathymine[60] from the thiosemicarbazone of pyruvic acid. An analogous procedure was later employed for preparing 6-azauracil (4,5-C^{14})[61] and a number of other 5-substituted derivatives.[62]

Using a single-step process, 6-azauracil can be prepared from chloral 3-methylisothiosemicarbazone (**59**). The apparent intermedi-

[58] E. A. Falco, E. Pappas, and G. H. Hitchings, *J. Am. Chem. Soc.* **78**, 1938 (1956).
[59] I. Nakata and T. Ueda, *Yakugaku Zasshi* **80**, 1068 (1960).
[59a] J. Slouka, *J. prakt. Chem.* **16**, 220 (1962).
[60] J. Gut, *Collection Czechoslov. Chem. Communs.* **23**, 1588 (1958).
[61] J. Morávek, *Collection Czechoslov. Chem. Communs.* **24**, 2571 (1959).
[62] J. Gut and M. Prystaš, *Collection Czechoslov. Chem. Communs.* **24**, 2986 (1959).

ate of this synthesis is the cyclic 3-methylmercapto derivative (**61**) which is immediately hydrolyzed in an acid solution (e.g., Section II,B,4,b). The yield in this synthesis is only 25%, however.[49]



b. Properties. It is well known that the 6-substituted dioxotriazines are monobasic acids titrated with phenolphthalein.[63,64] It was also known that they form salts but these have not been studied in detail.[48]

More recently the simplest member of this series, 6-azauracil, was investigated more thoroughly from this aspect.[21,65] Its dissociation constant was 7.00; it is thus considerably more acid than uracil ($pK_a = 9.43$). In the pH region above 10.0, a second hydrogen is also ionized. Uracil behaves in a similar manner.

Salts of 6-azauracil were studied in greater detail and their individual composition established.[65] 6-Azauracil, in common with uracil, is very resistant both toward acid and toward alkaline hydrolysis.

A detailed investigation of the tautomeric structure of 6-azauracil was carried out by Jonáš and Gut[66] and by Horák and Gut.[67] They measured the UV and IR spectra and compared similar systems and their derivatives in which the lactam or lactim configuration was fixed by *N*- or *O*-substitution (as will be seen later no *O*-alkyl deriva-

[63] E. Cattelain, *Bull. soc. chim. France* **12**, 59 (1945).
[64] E. Cattelain, *Ann. chim. anal.* **24**, 150 (1942); *Chem. Abstr.* **38**, 1971 (1944).
[65] J. Gut, M. Prystaš, J. Jonáš, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **26**, 974 (1961).
[66] J. Jonáš and J. Gut, *Collection Czechoslov. Chem. Communs.* **26**, 2155 (1961).
[67] M. Horák and J. Gut, *Collection Czechoslov. Chem. Communs.* **26**, 1680 (1961).

tives of 1,2,4-triazine have been prepared so far). It follows from these studies that 6-azauracil possesses a dilactam structure as was demonstrated earlier for uracil. Interpretation of the pH dependence of the UV spectra elucidated the sequence of dissociations in 6-azauracil and uracil (e.g., Section II,B,3,a).[21] The IR spectra of 6-azauracil and of its alkyl derivatives display two notable maxima in the carbonyl region.[67] In similar spectra of uracil and hydantoin this phenomenon was explained by the inequality of the two carbonyl groups. According to the shifts of frequency the maxima were attributed to the individual carbonyl groups.[68] A more acceptable interpretation explains the cleavage of the carbonyl band into two by the "coupling effect" of the two carbonyl groups.[67] The molecular diagrams of 6-azauracil, 5-azauracil, and uracil were calculated by the simple MO-LCAO method.[22] On the basis of these calculations the shifts of maxima in the UV spectra and some reactions of these compounds were explained.[23]

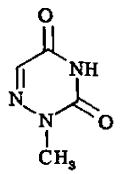
6-Azauracil and its alkyl derivatives are readily reducible by polarography, in contrast with uracil. This makes it possible to exploit the method analytically.[69] More detailed studies of the polarographic behavior of these substances are in good agreement with the results of spectral studies about the tautomeric form and type of dissociation.[70]

3. *N-Substituted Derivatives of 3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazines*

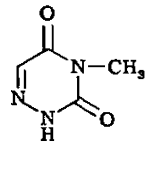
a. N-Alkyl Derivatives. The *N*-alkyl or aralkyl derivatives can be prepared by three procedures. First by direct alkylation, second by hydrolysis of *N*-alkylated 3-methylmercapto derivatives, and third, in some cases, by cyclization of substituted semicarbazones of α-keto acids.

It was observed already by Bougault[43,71] that the reaction of 6-benzyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazines with alkyl halides in an alkaline solution yields a mixture of the 4-mono- and 2,4-dialkyl derivatives. This mixture of alkylation products can be readily separated since the monoalkyl derivative is weakly acidic and therefore soluble in alkali whereas the dialkyl derivative is alkali-insoluble.[44] It was found by hydrolysis of the monoalkyl derivatives, resulting in 4-alkylsemicarbazones, that these were the 4-alkyl derivatives.[72,73] Alkaline alkylation has been used with a number of other 6-substituted derivatives.[45]

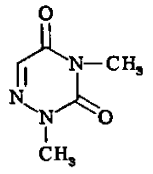
The alkylation of 6-azauracil will be treated later. The first, but not exactly identified dimethyl derivative was prepared by Grundmann.[40] The course of alkylation was studied in greater detail by Gut *et al.*[65] These authors found that in aqueous alkaline solution and on using alkyl halides or dialkyl sulfates, the main alkylation product is the 1,3-dialkyl derivative (**64**). Since, however, the alkylation is to some



[62]



[63]



[64]

extent accompanied by hydrolysis of the alkylation products, its course is not completely clear. Depending on the reaction conditions it is possible to isolate small amounts of the 1-alkyl (**62**) or 3-alkyl (**63**) derivatives from the mixture. The structure of the monoalkyl derivatives of 6-azauracil was defined by unequivocal synthesis of 1-methyl-6-azauracil (e.g., Section II,B,4,b). During similar alkylations of uracil no monoalkyl derivatives have been isolated.

The sodium or potassium salt of 6-azauracil in aqueous ethanol, anhydrous ethanol, or ethylene glycol reacted with methyl iodide practically exclusively to give the 3-methyl derivative (**63**). In toluene the sodium, potassium, and mercuric salts produced no methylated derivatives whereas the silver salt also yielded the 3-methyl derivative.[65] Similarly, the 3-methyl derivative was prepared from the mercuric salt of 6-azathymine, and its structure was established by hydrolysis to pyruvic acid 4-methylthiosemicarbazone.[74]

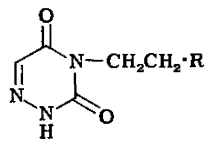
[68] H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structure." van Nostrand, New York, 1949.
[69] J. Krupička and J. Gut, *Collection Czechoslov. Chem. Communs.* **25**, 592 (1960).
[70] J. Krupička and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 546 (1962).
[71] J. Bougault, *Compt. rend. acad. sci.* **159**, 83 (1914).
[72] E. Cattelain, *Compt. rend. acad. sci.* **208**, 1656 (1939).
[73] J. Bougault, *Compt. rend. acad. sci.* **160**, 625 (1915).
[74] R. H. Hall, *J. Am. Chem. Soc.* **80**, 1145 (1958).

During methylation of 6-azauracil with a theoretical amount of diazomethane, the 3-methyl derivative (**63**) was obtained in very good yield. Excess reagent produces the dimethyl derivative (**64**). During none of the alkylation reactions was it possible to observe the formation of *O*-alkyl derivatives of 6-azauracil.[65] This can be taken as evidence that 6-azauracil does not react in the lactim form (e.g., Section II,B,2,b).

The course of alkylations of 6-azauracil is in good agreement with the results of determination of the dissociation constants of 6-azauracil and of its two monomethyl derivatives.[21,65] On the assumption that a methyl group does not much affect the dissociation constant, and on the basis of the lactam structure, it may be concluded from the values of the dissociation constants (pK_a of 6-azauracil = 7.00, of 1-methyl-6-azauracil = 6.99, and of 3-methyl-6-azauracil = 9.52) that dissociation takes first place at the NH group in position 3. The same results are obtained independently by comparing the pH dependence of the UV spectra of these compounds.[66] These results represent an exact confirmation of the older observation by Cattelain[63] that the monoalkyl derivatives of 6-substituted dioxotriazines possess different acidity.

It should be mentioned that a similar comparison of the dissociation constant values of uracil monoalkyl derivatives does not permit the determination of the sequence of dissociation on account of the small differences between the pK_a values.[65] However, the pH dependence of the UV spectra showed that the first dissociation of uracil occurs at the NH group in position 1 and thus differently than in 6-azauracil.[66] This, together with different acidity, represents the main differences between the properties of uracil and its 6-aza analogs.

The reaction of ethylene carbonate with acid imides[75] which yields *N*-hydroxyethyl derivatives was applied to 6-azauracil. In agreement with the foregoing findings, 6-azauracil produced a 3-(2-hydroxyethyl) derivative (**65**) which was treated with thionyl chloride to convert



[65] : R = OH
[66] : R = Cl

[75] K. Yanagi and S. Akiyoshi, *J. Org. Chem.* **24**, 1122 (1959).

it to the 3-chloroethyl derivative (**66**). On applying the aforementioned reaction to uracil, a mixture of 1-(2-hydroxyethyl) and 1,3-bis-(2-hydroxyethyl) derivatives was produced.[76]

The preparation of *N*-alkyl derivatives of 6-benzyl-3,5-dioxo-1,2,4-triazine by hydrolysis of the corresponding alkylmercapto derivatives was systematically studied by Cattelain.[54,77,78] The conversion to known alkyl derivatives of dioxotriazines was used to determine the structure of alkylated methylmercapto derivatives. As will be shown later (e.g., Section II,B,4,b) this procedure has a general preparative significance for 1-alkyl derivatives of 6-azauracil.[79]

Hydrolytic cleavage of the methylmercapto group usually proceeds very readily and in practically quantitative yield even on short boiling in water acidified with a few drops of hydrochloric acid. The readiness of the hydrolysis can be affected very substantially by substitution as shown in the case of 4-methyl-3-methylmercapto-5-thioxo-4,5-dihydro-1,2,4-triazine which was hydrolyzed only with 3*N* hydrochloric acid.[80]

This method can be considered as a general one except when the preparation of methylmercapto derivatives is not possible, e.g., with 6-benzyl-2,4-dimethyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine which was converted to the corresponding dioxotriazine derivative by oxidation with bromine in an alkaline solution.[81]

The last of the procedures of preparation of *N*-alkyl derivatives of dioxotriazines is the cyclization of *N*-alkylated semicarbazones of α-keto acids. It was employed only in a few cases and it appears that its yields are very low.[72,82,83] Despite the fact that even here a fundamental effect of substitution on the yield of cyclization can be expected, as the case is with analogous thiosemicarbazones (e.g., Section II,B,4,b), the method is of no particular preparative value.

The IR and UV spectra of the *N*-alkyl derivatives of 6-azauracil[66,67]

[76] M. Prystaš and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 1054 (1962).
[77] E. Cattelain, *Bull. soc. chim. France* **11**, 249 (1944).
[78] E. Cattelain, *Bull. soc. chim. France* **11**, 273 (1944).
[79] J. Gut, M. Prystaš, and J. Jonáš, *Collection Czechoslov. Chem. Communs.* **26**, 986 (1961).
[80] M. Prystaš and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 1898 (1962).
[81] E. Cattelain, *Bull. soc. chim. France* **12**, 39 (1945).
[82] E. Cattelain, *Bull. soc. chim. France* **12**, 53 (1945).
[83] E. Cattelain, *Compt. rend. acad. sci.* **207**, 998 (1938).

are essentially identical with the spectra of 6-azauracil. In the IR spectrum, alkylation brings about characteristic shifts of frequency of one or the other maximum in the carbonyl region. This can be employed for defining the substitution site. The differences in the pH dependence of the UV spectra are of similar significance.

b. N-Acyl Derivatives. 6-Benzyl-[82] and 6-styryl-dioxotriazines[84] were found to form acetyl derivatives, but the position of the acetyl group has not been determined. Mono-acetyl derivatives of 6-azauracil (**67**) and of 6-azathymine were described by Prystaš *et al.*[85,86] Since methylation of these acetyl derivatives with diazomethane and subsequent hydrolysis of the methylation products (**68**) yielded the well-known 3-methyl-6-azauracil (**63**), it was concluded that the acetyl was bound in position 1. It can be assumed that the same position (2 of the triazine ring) is also occupied in the other acetyl derivatives mentioned. 1-Acetyl-6-azauracil readily loses the acetyl group on treatment with water or alcohol. This makes it possible to employ the acetylation for reversible masking of position 1.

Acetylation of 6-azauracil thus proceeds in the same way as the acetylation of uracil[87] and the properties of the acetyl derivatives are also roughly identical.

c. Nucleosides. The ribofuranosyl and 2′-deoxyribofuranosyl derivatives of 6-azauracil and 6-azathymine represent now the most important compounds of this group from the point of view of biochemistry.

Some of them were obtained for the first time by an enzymatic procedure which, of course, can result only in the aza analogs of natural nucleosides, i.e., ribofuranosyl-6-azauracil (6-azauridine) (**75**) and 2′-deoxyribofuranosyl-6-azathymine (6-azathymidine). The first of these was prepared by Škoda *et al.*[88] and a modification of their procedure was used by Handschumacher.[89] In this way it is possible to obtain the crystalline nucleoside on the large scale.

[84] S. Bodforss, *Ann. Chem. Liebigs* **639**, 125 (1961).
[85] M. Prystaš, J. Gut, and F. Šorm, *Chem. & Ind. (London)* p. 947 (1961).
[86] M. Prystaš, J. Gut, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **27**, 1572 (1962).
[87] L. B. Spector and E. B. Keller, *J. Biol. Chem.* **232**, 185 (1958).
[88] Škoda, V. F. Hess, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **22**, 1330 (1957).
[89] R. E. Handschumacher, *Nature* **182**, 1090 (1958).

6-Azathymidine was first prepared by Prusoff[90] and the procedure was described in more detail by Hall and Haselkorn.[91] The nucleoside was prepared here in the form of a glassy solid, but with dibenzylphosphochloridate it yielded a mixture of nucleotides from which crystalline 3′-phosphate, 5′-phosphate, and 3′,5′-diphosphate were prepared.

By comparing the dissociation constant of 6-azauracil and 6-azauridine with those or uracil and uridine, 6-azauridine is now considered to be 1-ribofuranosyl derivative (2-ribofuranosyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine).[92] The same was shown more exactly by comparing the UV and IR spectra and the dissociation constants of 6-azauridine with the two monomethyl derivatives of 6-azauracil.[79,80] Enzymatic synthesis thus, proceeds, in the same way in natural bases and in their aza analogs.

The first chemical synthesis of these substances, using a procedure which yields 1-ribofuranosyl derivatives by pyrimidine bases, was described by Hall.[93] By using the mercuric salt of 6-azathymine and tribenzoate of D-ribofuranosyl chloride, he obtained a mixture of two monoribosyl derivatives and a diribosyl derivative. He determined the structure of the 3-substituted derivative by the similarity of spectra and other properties to those of 3-methyl-6-azauracil. The structure of the 1-ribosyl derivative was then determined from the similarity of the spectra with 6-azathymine deoxyriboside obtained enzymatically.

Handschumacher[92] applied a similar procedure to 6-azauracil and obtained a mixture of two monoribosyl derivatives from the mercuric salt of 6-azauracil, with the 3-substituted derivative predominating.

Chemical and enzymatic ribosidization of the aza analogs of the pyrimidine bases thus take different routes. These results and independent earlier studies of the alkylation of 6-azauracil[65] led to the conclusion that, in order to achieve ribosidization in position 1 (i.e., position 2 of the triazine ring), the position 3 (4 of the triazine ring) must be protected.[92,80]

This procedure was verified by synthesizing 3-methyl-6-azauridine

[90] W. H. Prusoff, *J. Biol. Chem.* **215**, 809 (1955).
[91] R. H. Hall and R. Haselkorn, *J. Am. Chem. Soc.* **80**, 1138 (1958).
[92] R. E. Handschumacher, *J. Biol. Chem.* **235**, 764 (1960).
[93] R. E. Hall, *J. Am. Chem. Soc.* **80**, 1145 (1958).

tribenzoate (**69**) as described by Prystaš *et al.*[80] 1-Acetyl-6-azauracil was methylated with diazomethane to obtain authentic 3-methyl-6-azauracil, and its salt was converted in the usual way to 3-methyl-6-azauridine tribenzoate. An identical product was obtained by methylation of tribenzoate of natural 6-azauridine (**70**) with diazomethane. This confirmed the assumption that 6-azauridine is actually a 1-ribofuranosyl derivative. On the assumption that the steric course of ribosidization studied in detail in the pyrimidine bases is the same as in their aza analogs, 6-azauridine is 1-β-D-ribofuranosyl-6-azauracil.

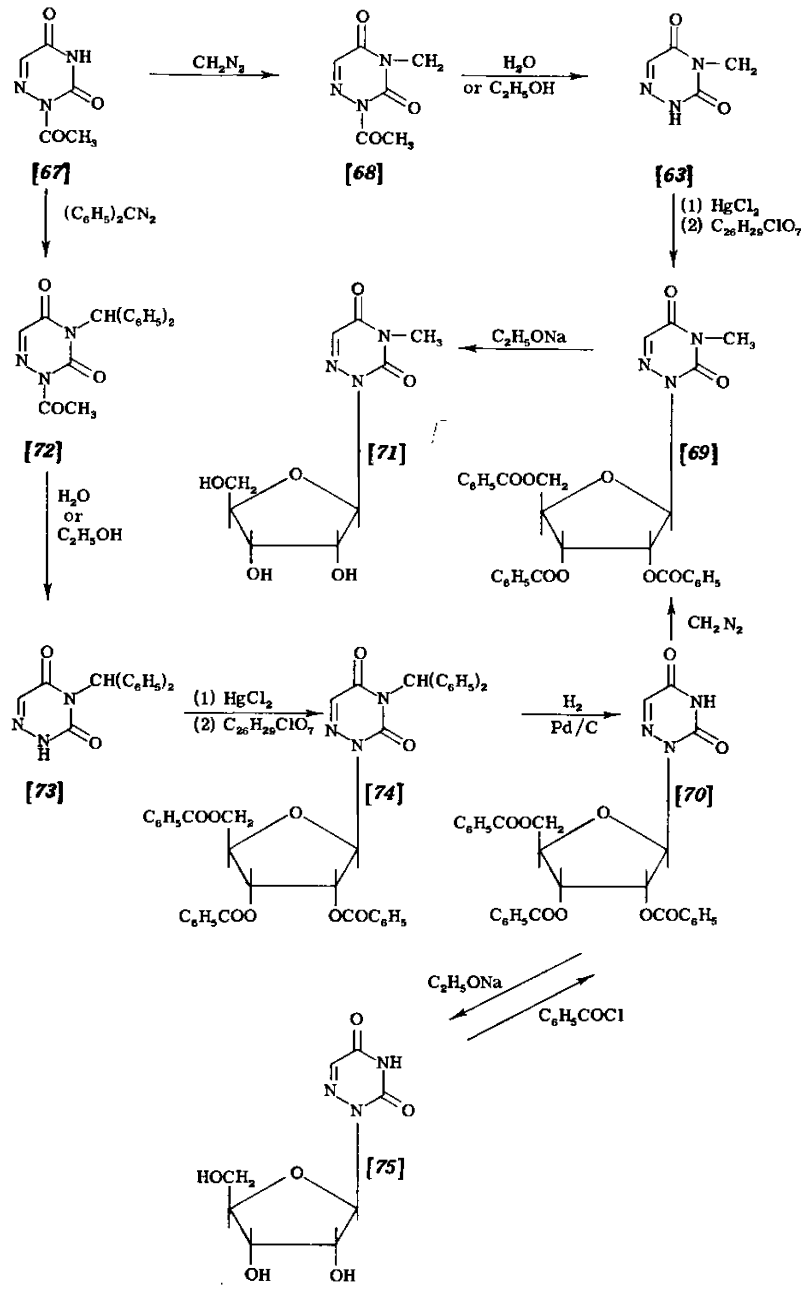
By reversibly blocking position 3 with a diphenylmethyl group (**72, 73**), Prystaš and Šorm[94] also prepared 6-azauridine. The diphenylmethyl group was removed after ribosidization (**74**) by selective hydrogenolysis. The crystalline 6-azauridine obtained was identical with 6-azauridine prepared enzymatically.[88]

This synthesis appears to be quite general for the preparation of 1-substituted nucleosides and was used with small modifications for the synthesis of 1-ribofuranosyl-6-azathymine[94] and 2′-deoxyribofuranosyl-6-azauracil[95] and -6-azathymine.[96] In the case of 2′-deoxyribofuranosyl a mixture of α- and β-anomers is produced, their ratio depending on the reaction conditions. In the preparation of 2′-deoxyribofuranosyl-6-azathymine only one anomer was obtained having probably the β-configuration.[96]

6-Azauridine was also synthesized using the knowledge of the course of alkylation of 6-azauracil 2-methylmercapto derivatives[79] (e.g., Section II,B,4,b). The 1-ribofuranosyl derivative obtained by reaction of the mercury salt of the 2-methylmercapto derivative with tri-*O*-benzoyl-β-D-ribofuranosyl chloride on removal of the methylmercapto and then benzoyl groups yielded crystalline 6-azauridine.[96a]

The main difference between uracil and 6-azauracil nucleosides consists in the preparation of cyclic nucleosides. It is known that uridine can be readily converted to cyclic nucleosides by the reaction of 2′(5′)-*O*-mesyl derivatives with nucleophilic agents.[97] Analogous

[94] M. Prystaš and F. Šorm, *Collection Czechoslov. Chem. Communs.* **27**, 1578 (1962).
[95] J. Pliml and F. Šorm, *Chem. & Ind. (London)*, p. 655 (1962).
[96] J. Pliml, M. Prystaš, and F. Šorm, *Collection Czechoslov. Chem. Communs.*, in press.
[96a] A. R. Restivo and F. A. Dondzila, *J. Org. Chem.* **27**, 2281 (1962).
[97] D. M. Brown, D. B. Parihar, and A. Todd, *J. Chem. Soc.* p. 4242 (1958).

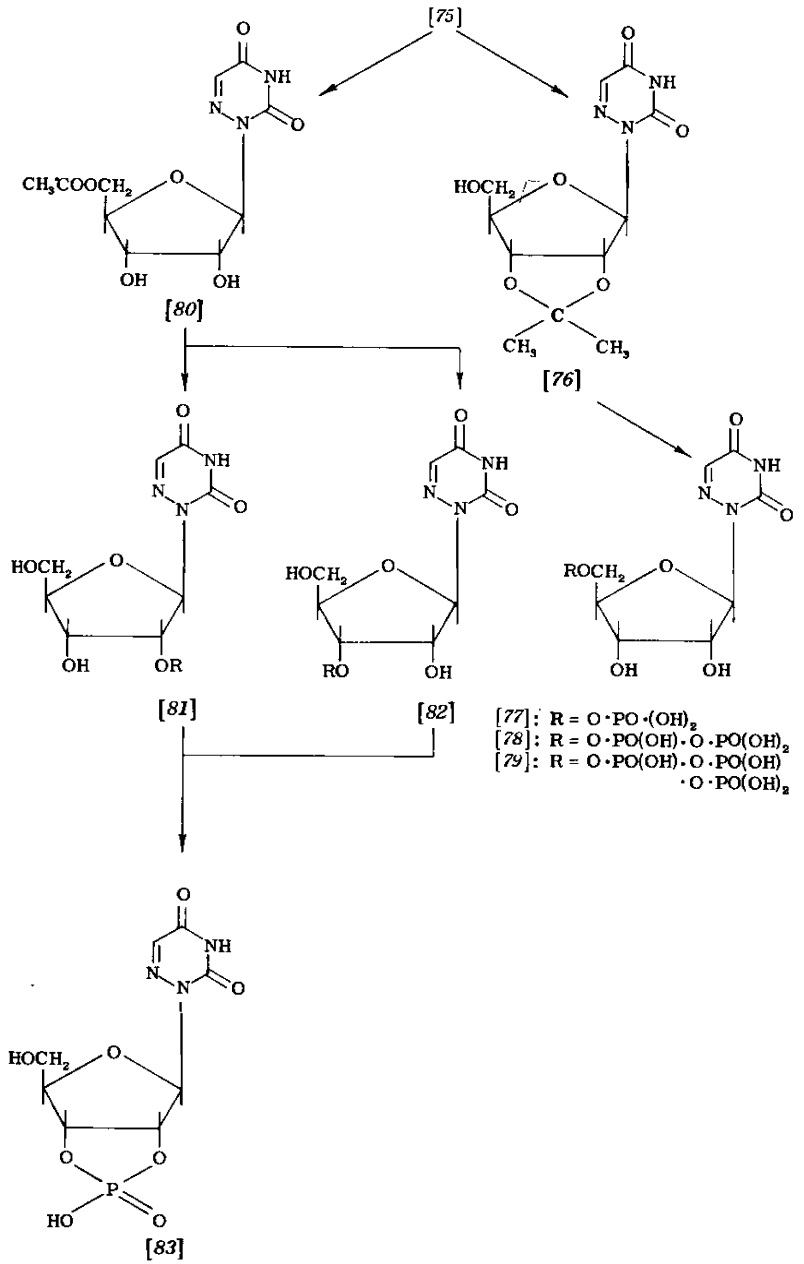


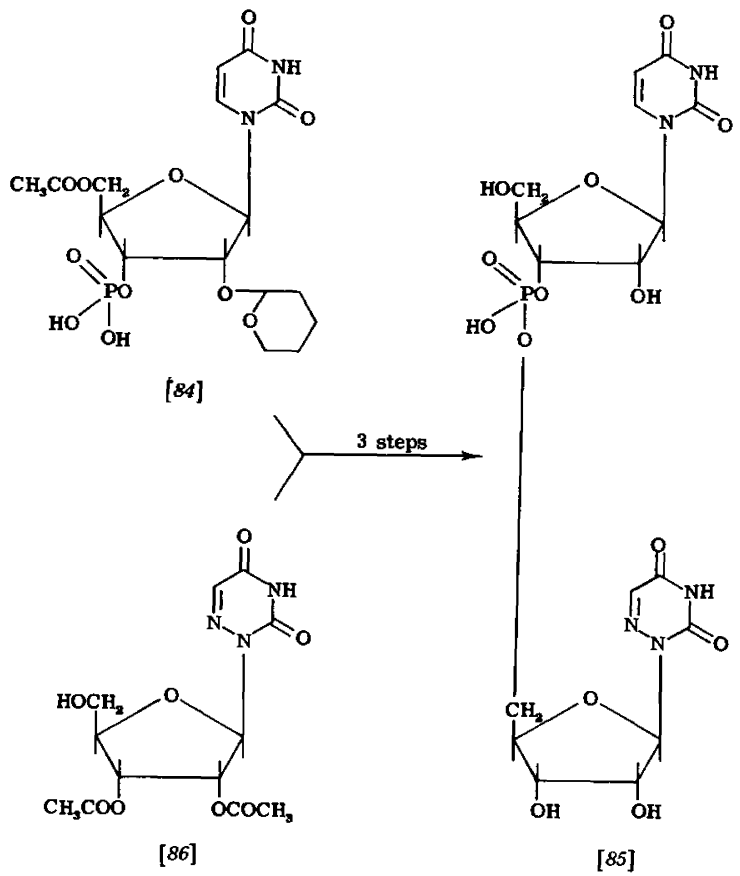
derivatives of 6-azauridine have not yet been cyclized by such agents. It was also attempted, unsuccessfully, to convert 6-azauridine[98] to an $O^2,2'$-cyclonucleoside, which is relatively simple to achieve with uridine and cytidine by means of polyphosphoric acid.[99] These results can be taken as further evidence that 6-azauracil does not react in the lactim form.

d. Nucleotides. Beside the aforementioned preparation of 6-azathymidine nucleotides, procedures for the preparation of individual 6-azauracil nucleotides were developed by Smrt, Šorm, and coworkers. The 5′-phosphoryl derivatives were prepared from 2′,3′-*O*-isopropylidene-6-azauridine (**76**) by treatment with dibenzylphosphochloridate, with tetra-*p*-nitrophenylphosphate, or with polyphosphoric acid.[100,101] The 5′-diphosphate (**78**) was prepared from the monophosphate (**77**) by the action of dibenzylphosphochloridate,[100,101] the 5′-triphosphate (**79**) from 6-azauridine-5-phosphomorpholidate and pyrophosphoric acid.[102]

Proceeding from 5′-*O*-acetylazauridine (**80**), a mixture of 2′- and 3′-monophosphates (**81**, **82**) was prepared by phosphorylation with polyphosphoric acid, and these were converted into the 2′,3′-cyclic phosphate (**83**).[101] From the 2′,3′-*O*-isopropylidene derivative of 3-methyl-6-azauridine the 5′-phosphate was prepared by treatment with cyanoethylphosphate and the corresponding diphosphate from its morpholidate through the action of phosphoric acid.[103] Furthermore, a diribonucleoside phosphate (**85**) with a natural 3′-5′ internucleotide linkage was prepared from 6-azauridine. The starting material for the preparation of such derivatives was 5′-*O*-acetyl-2′-*O*′-tetrahydropyranyluridine-3′-phosphate (**84**) which was condensed with 2′,3′-di-*O*-acetylazauridine (**86**) or with 2′,3′-*O*-isopropylidene-6-azauridine (**76**) with the aid of dicyclohexylcarbodiimide.[104]

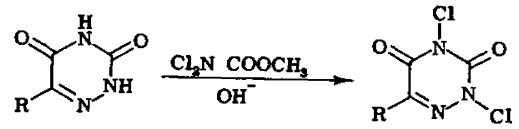
[98] J. Smrt, private communication (1961).
[99] E. R. Walwick, W. K. Roberts, and C. A. Dekker, *Proc. Chem. Soc.* p. 84 (1959).
[100] J. Smrt, J. Beránek, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **25**, 130 (1960).
[101] J. Beránek and J. Smrt, *Collection Czechoslov. Chem. Communs.* **25**, 2029 (1960).
[102] J. Žemlička, J. Smrt, and F. Šorm, *Collection Czechoslov. Chem. Communs.*, in press.
[103] J. Žemlička, J. Smrt, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **27**, 1462 (1962).
[104] J. Smrt and F. Šorm, *Collection Czechoslov. Chem. Communs.* **27**, 73 (1962).





[84] [86] [85]

e. Other N-Substituted Derivatives. The *N*-substituted derivatives also include the 6-substituted 2,4-dichloro-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazines (87) prepared by the action of esters of *N,N*-dichloro-



[87]

carbamic acid.[105,106] For 6-azauracil itself, and in more recent times for its derivatives too, no mention of such compounds can be found in the literature.

4. *Sulfur Derivatives*

The derivatives of dioxo-1,2,4-triazines in which one or both oxygen atoms are replaced with sulfur do not represent analogs of natural bases of nucleic acids. As was mentioned before, however, they occur as frequent intermediates during the preparation of dioxotriazines and are, therefore, mentioned briefly in this connection.

a. Thioxo Derivatives. Cyclization of thiosemicarbazones of α-keto acids with aqueous alkali represents the common method for the preparation of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines[52,53] as was mentioned earlier (e.g., Section II,B,2,a). Similarly to the semicarbazones, the cyclization is affected here by substituents in the α-position. The yields are then generally higher, so that the aryl or aralkyl derivatives are formed in a practically quantitative yield; even for the lowest homologs and glyoxylic acid thiosemicarbazone itself yields are still rather good.[60]

Formerly the required amount of hydroxide (usually in the form of 1 *N* solution) was added until alkaline to phenolphthalein plus some excess. Cyclization was achieved either at normal temperature (several days or weeks) or by boiling for several hours.

It was found recently that the cyclization requires the application of 2 moles of alkaline hydroxide; in practice, a small excess was used. It was demonstrated that the cyclization is termined within 15 min, and even sooner with α-aryl or 2-*N*-alkyl derivatives.[79]

The preparation of the 6-propyl to 6-undecyl derivatives, however, was performed by boiling for 30 min with potassium carbonate.[59] Sodium methoxide in a mixture of ethanol and benzene was used for the cyclization of the thiosemicarbazone of phenylglyoxylic acid ester.[107]

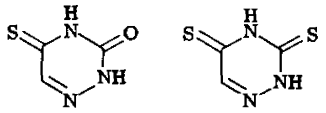
The ease of cyclization of the α-monothiosemicarbazone of benzoylpyruvic acid seems to be exceptional; it was carried out either with

[105] J. Bougault and P. Chabrier, *Compt. rend. acad. sci.* **213**, 400 (1941).
[106] P. Chabrier, *Ann. chim. (Paris)* **17**, 353 (1942); *Chem. Abstr.* **38**, 3255 (1944).
[107] G. H. Hitchings, P. B. Russell, and A. D. Maggiolo, German patent 951,996 (1956); *Chem. Abstr.* **53**, 13186 (1959).

aqueous hydroxide or with dilute acetic acid or even with ethanol alone.[108]

The numerous 6-substituted 3-thioxo-5-oxo derivatives prepared by earlier authors are reviewed by Erickson *et al.*[109] Subsequently a number of alkyl,[58,61] and further 4-acetaminophenyl, 2-thienyl, 4-pyridyl,[110] 4-antipyryl,[111] and 2-aminoethyl[112] derivatives were prepared plus some others mentioned in the section on the synthesis of 6-azauracil.

5-Thioxo-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (4-thio-6-azauracil) (**88**) and 3,5-dithioxo-2,3,4,5-tetrahydro-1,2,4-triazine (2,4-dithio-6-azauracil) (**89**) were prepared by Hitchings *et al.*[58] treating 6-aza-



[*88*]

[*89*]

uracil with phosphorus pentasulfide. The mixture of the two substances formed simultaneously was resolved by ion-exchange chromatography. It was found later that by thiation of 6-azauracil under suitable conditions the 5-thioxo derivative can be obtained practically pure.[79] For the same reason it is advantageous to prepare the 3,5-dithioxo derivative from the 3-thioxo derivative.[79,113] The effect of the ratio of the starting compounds, the quality of phosphorus pentoxide, and the reaction time was examined by Jacquier and Lieberman.[113] The difference between the reactivity of both the carbonyl groups seems to be more pronounced in 6-azauracil than in uracil.[114]

The course of thiation (replacement of oxygen by sulfur) of dioxo-

[108] G. La Parola and C. J. Turi, *Ann. chim. (Rome)* **51**, 283 (1961).
[109] J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," Vol. 10 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 79. Interscience, New York, 1956.
[110] R. E. Hagenbach, E. Hodel, and H. Gysin, *Experientia* **10**, 62 (1954); *ibid.* **11**, 314 (1955).
[111] F. Schmidt, *Arch. Pharm.* **289**, 150 (1956).
[112] J. Hadáček and J. Slouka, *Pharmazie* **13**, 402 (1958).
[113] D. Liebermann and R. Jacquier, *Bull. soc. chim. France* p. 383 (1961).
[114] H. L. Wheeler and L. M. Liddle, *Am. Chem. J.* **40**, 547, 557 (1908).

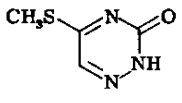
triazines is considerably affected by substitution in the ring. In the case of thiation of 6-azathymine only the dithio derivative was obtained.[58] With other 5-alkyl or aryl derivatives the reaction has not been tried. The effect of *N*-substitution is more complicated.[79] 1-Methyl-6-azauracil yielded 1-methyl-2,4-dithio-6-azauracil; 1-ribofuranosyl-6-azauracil tribenzoate[115] produced only the 4-thio derivative. Thiation of 3-methyl-6-azauracil resulted in a mixture of 4-thio and 2,4-dithio derivatives with a clear predominance of the former. 1,3-Dimethyl-6-azauracil yielded only the 4-thio derivative under the same conditions. The 2-thio and the 2-methylmercapto derivatives yield the corresponding dithio and 2-methylmercapto-4-thio derivatives irrespective of further substituents.[79]

Thiation was most frequently carried out in pyridine[58,113]; for unsubstituted compounds which are considerably polar, this is a prerequisite. The less polar *N*-alkylated derivatives can be thiated in toluene or xylene[79]; for thiation of 6-azathymine, tetralin was also used.[116]

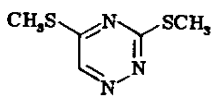
b. S- and N-Alkyl Derivatives. The alkylation of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine was studied systematically by Cattelain[54,77,78] using 6-substituted derivatives, mostly benzyl. He found that their alkylation in an alkaline medium results first in 3-alkyl derivatives and subsequently in the 2,3-dialkyl ones. He concluded that these compounds react in the thiol form and that the methylmercapto derivatives formed have structure (**96**) (with a double bond in position 3,4). In addition to the investigation of the reduction of these substances with amalgam[63] (the interpretation of which is not completely convincing), he found that 3-thioxo derivatives are oxidized to disulfides.[56,117]

Alkylation reactions were recently performed with all the thio derivatives of 6-azauracil and 6-azathymine.[79] In agreement with previous findings, the methylmercapto derivatives were obtained by alkylation of all these substances in alkaline solution. Thus, e.g., 3-methylmercapto-5-oxo-2,5-dihydro-1,2,4-triazine (**96**), 5-methylmercapto-3-oxo-2,3-dihydro-1,2,4-triazine (**90**), and 3,5-dimethylmercapto-1,2,4-triazine (**91**) were obtained. The last-named of these was

[115] V. Černěckij, S. Chládek, F. Šorm, and J. Smrt, *Collection Czechoslov. Chem. Communs.* **27**, 87 (1962).
[116] Burroughs Wellcome & Co., British patent 802,122 (1958); *Chem. Abstr.* **53**, 7216 (1959).
[117] E. Cattelain, *Compt. rend. acad. sci.* **215**, 257 (1942).



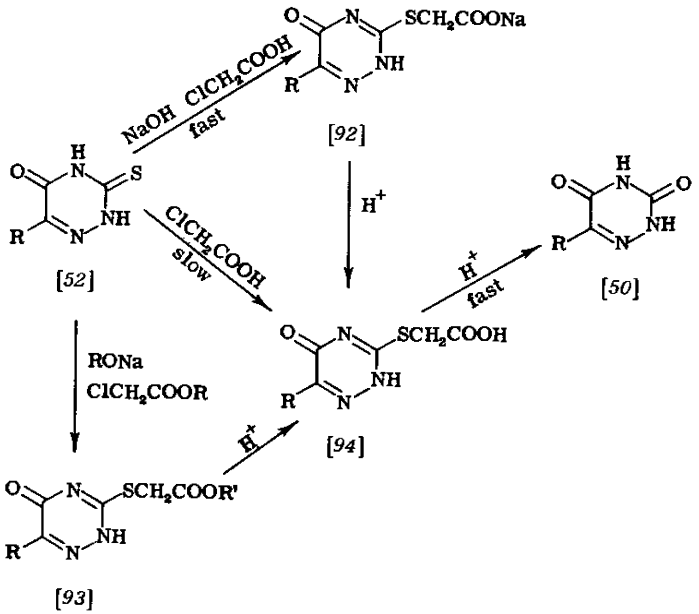
[90]



[91]

also prepared from 3,5-dichloro-1,2,4-triazine[41] (cf. Section II,B,6). All these reactions take place in aqueous hydroxide or in alcoholic sodium ethylate, at normal temperature.

In this connection the course of the reaction of 3-thioxo derivative (**52**) with chloroacetic acid was studied in detail,[62] the reaction being important for the transformation to dioxotriazine derivatives. In this reaction, the carboxymethylmercapto derivatives (**94**) must be expected as intermediates. The ethyl esters of these compounds (**93**) ($R = CH_2C_6H_5$; $R' = C_6H_5$) were isolated by Cattelain after reaction with ethyl chloroacetate.[55] When the reaction is performed in the usual preparative way using 10% aqueous solution of chloroacetic acid, it requires 3–5 hr of boiling. In an alkaline solution (with a



total of 3 equivalents of NaOH), the reaction proceeds considerably more rapidly and stops at the sodium salt stage (**92**). From the substituted derivatives (R = alkyl or aryl), free carboxymethylmercapto derivatives (**94**) can be obtained, which are relatively stable in neutral solution. In an acid solution they are rapidly hydrolyzed to the dioxo derivatives (**50**). During the reaction with aqueous chloroacetic acid the slow substitution reaction is the rate-determining step. The unsubstituted carboxymethylmercapto derivative (**94**; R = H) is hydrolyzed immediately after liberation from its salt and was isolated only in the form of an ester (**93**; R = H).[62]

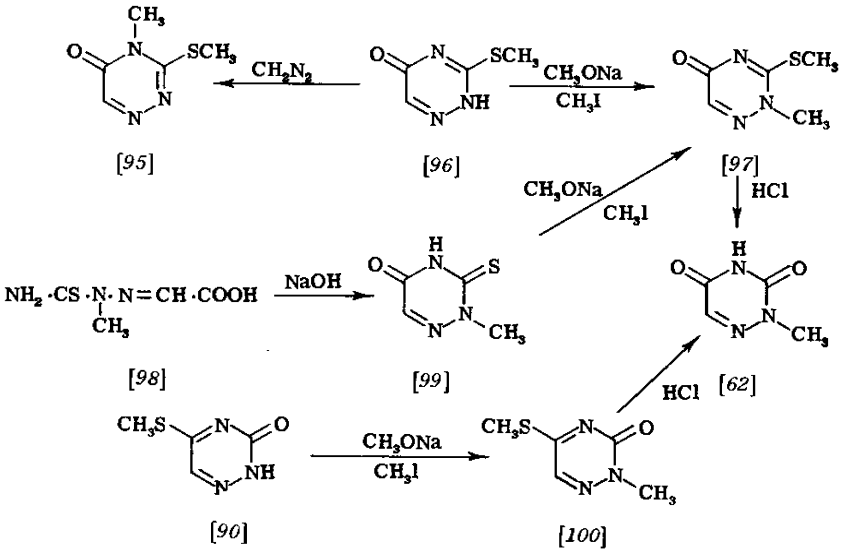
In agreement with the results of Cattelain, further methylation of the 3-methylmercapto derivative (**96**) results practically exclusively in 2-methyl-3-methylmercapto-5-oxo-2,5-dihydro-1,2,4-triazine (**97**). Further methylation of 5-methylmercapto derivative (**90**) yields 2-methyl-5-methylmercapto-3-oxo-2,3-dihydro-1,2,4-triazine (**100**). Their structure was confirmed by acid hydrolysis leading to 2-methyl-3,5-dioxo derivatives (**62**). As was already mentioned, this reaction is a suitable general procedure for preparing the 1-alkyl derivatives of 6-azauracil.[79]

The course of methylation of all the thio derivatives with diazomethane was then investigated.[79,80] These methylations generally result in mixtures of substances; it may be deduced from the products isolated, however, that this reaction proceeds first at the nitrogen atom (in contrast with alkaline methylation) and only then at the sulfur one. The methylation of the 3-methylmercapto derivative to 4-methyl-3-methylmercapto-5-oxo-4,5-dihydro-1,2,4-triazine (**95**) is of interest in this connection.

Some alkylated derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines were also prepared by cyclization of the corresponding substituted thiosemicarbazones of α-keto acids. During these cyclizations a very marked effect of alkylation on the yield and course of the reaction can be observed.

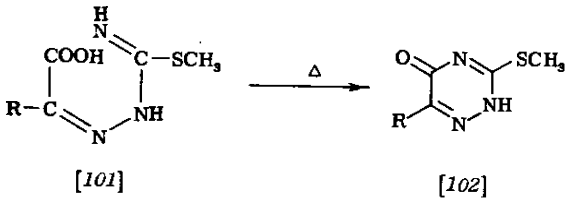
A uniformly favorable effect is displayed by an alkyl group, in position 2. Thus the 2-methylthiosemicarbazone of pyruvic acid is cyclized at normal temperature and without excess hydroxide.[54,118] The 2-methylthiosemicarbazone of glyoxylic acid (**98**) was cyclized by boiling for 5 min to 2-methyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (**99**) (yield 93% as compared with 70–80% in the un-

[118] E. Cattelain, *Compt. rend. acad. sci.* **210**, 301 (1940).



substituted derivative[60]). This reaction was used for an unambiguous synthesis of 1-methyl-6-azauracil.[65]

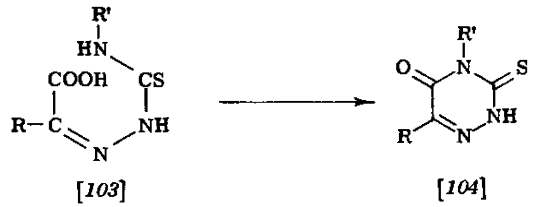
Alkylation in position 3 has a still more pronounced effect. The thiosemicarbazones (**101**) obtained here were prepared either from 3-methylisothiosemicarbazide hydroiodide or by methylation of thiosemicarbazones. Their cyclization was performed either by boiling in alcohol or by heating to the melting point (**102**).[54,96a] The presence of



alkalies, in contrast with the preceding reactions, prevented cyclization.[54] A similar course is probably followed by the reaction of 3-methylisothiosemicarbazide with chloral[49] mentioned in the foregoing (cf. Section II,B,2,a). Hence it might be concluded that the cyclization requires the formation of the thiol form of the starting thiosemicarbazone which is present in an alkaline medium or which can be fixed by substitution on the sulfur atom.

Substitution in position 4 displays a more complex influence. Cyclization of the 4-methyl- and 4-ethyl-thiosemicarbazones of phenylpyruvic acid and of the 4-methylthiosemicarbazone of phenylglyoxylic acid (**103**) was readily achieved[78] (**104**), whereas it was not possible to cyclize the analogous 4-methyl derivatives of pyruvic[119] and glyoxylic acids.[65] It thus appears that cyclization is hindered by substitution in position 4 and that this unfavorable effect can be partly relieved by the known favorable effect of an aryl or aralkyl group in the α-position.

The cyclization of the 4-methylthiosemicarbazone of pyruvic acid was recently effected by refluxing in dimethylformamide.[119a]

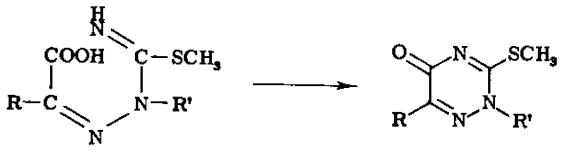


It can be concluded from further results, however, that the nature of the substituent in position 4 is even of more importance. Thus the 4-benzylthiosemicarbazone of phenylpyruvic acid is not cyclized[78] whereas 4-arylthiosemicarbazones of pyruvic acid and phenylglyoxylic acid are readily cyclized merely by boiling in ethanol, in the absence of alkalies. Attempted alkaline cyclization, on the contrary, results in the original product or (in the case of glyoxylic acid derivative) it is split to phenylthiourea.[120] Among other examples, the cyclization of the 4-methylthiosemicarbazone of cinnamoylformic acid in low yield should be mentioned. Cyclization of the 4-phenylthiosemicarbazone of the same acid proceeded readily on boiling in ethanol, and during the usual alkaline cyclization conditions the 4-phenylthiosemicarbazone of benzaldehyde was formed.[84]

As may be expected on the basis of the preceding results, the cyclization of 2,3-dialkylthiosemicarbazones (**105**) will take place

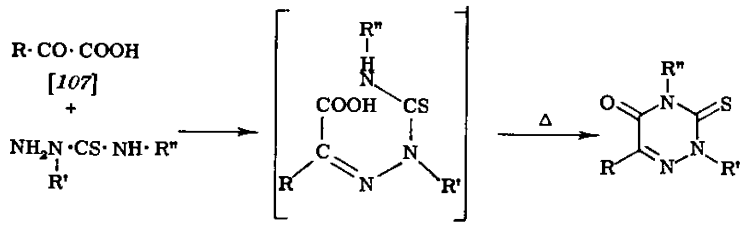
[119] R. Jacquier, private communication, (1961).
[119a] K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.* **27**, 976 (1962).
[120] M. Tišler and Ž. Vrbaški, *J. Org. Chem.* **25**, 770 (1960).

very readily[81] (**106**). It is harder to explain why the 3,4-dialkyl derivatives are not cyclized[81] and why the 2,4-dialkyl ones, on the contrary, undergo cyclization even on mixing the substituted semi-



[*105*] [*106*]

carbazide (**108**) with phenylpyruvic acid (**107**) without isolating the thiosemicarbazone (**109**) formed.[81] In the case of 2-phenyl-4-methyl-thiosemicarbazide and of pyruvic acid, the cyclization set in just on boiling in ethanol or in acetic acid.[121] In the same way, the cor-



[*108*] [*109*] [*110*]

responding triazine was obtained from cinnamoylformic acid and 2,4-diphenylthiocarbazide.[84]

The cyclization of some 2- and 4-methylthiosemicarbazones and the thiation of the cyclic product was recently studied by Zee-Cheng and Cheng.[119a]

Even if no general conclusions can be drawn on the basis of existing material, it appears that further study of cyclization of these substances could elucidate the mechanism of cyclization of thiosemicarbazones of α-keto acids which is of fundamental importance in the chemistry of dioxotriazines.

c. Properties. On the basis of reactions of the 3-thioxo derivatives, especially of the ready alkylation on sulfur, a thiol structure was

[121] J. A. Elvidge and F. S. Spring, *J. Chem. Soc., Suppl.* No. 1, S 135 (1949).

formerly attributed to these substances.[45,63] Tišler and Vrbaški recently studied the UV and IR spectra of a series of 2,6-disubstituted 3-thioxo-5-oxotriazines and in neutral solution ascribed to them the thioxo form. In alkaline medium the anionic charge resides predominantly on the sulfur atom so that alkylation affords alkylmercapto derivatives.

The aforementioned detailed studies of the methylation of thio analogs of 6-azauracil[79,80] made it possible to obtain a practically complete set of all structural types, fixed in the thiolactam or thiol form. This enabled a detailed study of the structure of these substances by UV spectra.[122] It was shown that all the thio analogs of 6-azauracil possess the thioxo form in neutral solution. Similar results are indicated by the IR spectra of all the thioxo derivatives which show absorption peaks for the free NH group in the lactam region and for the thioxo grouping.[123] The UV spectra also show that the 3-methylmercapto derivative has the structure (**96**) with a double bond in position 3,4. In agreement with this finding is its further methylation in position 2 (**97**) in an alkaline medium. It is of interest that with the UV spectra, the *S*- and *N*-substituted derivatives exhibit marked differences[122]; the analogous *O*- and *N*-substituted derivatives of this type of substances display only insignificant differences (see e.g., Section II,A,2,b).

It was found already by Cattelain[63] that the 3-thioxo derivatives behave as monobasic acids that can be titrated on phenolphthalein and he considered them as more acid than the analogous 3,5-dioxo-triazines. This assumption was recently confirmed by determining the dissociation constants. Just as with 6-azauracil, it was possible to demonstrate, by comparing the dissociation constants of the *N*-methyl derivatives of all the thioxo analogs, that with the 3-thioxo compounds too, dissociation proceeds first at the NH group in position 3.[122]

5. *6-Substituted Derivatives of 3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazine*

6-Alkyl and 6-aryl derivatives of 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine or of its thio analogs have been mentioned before in this review (e.g., Section II,B,2,a). Some of them contained functional

[122] J. Jonáš and J. Gut, *Collection Czechoslov. Chem. Communs.* **27**, 1886 (1962).
[123] M. Horák and J. Gut, *Collection Czechoslov. Chem. Communs.*, in press.

groups at the more distant positions of the alkyl or aryl group. This is obviously no obstacle for their formation by cyclization of semicarbazones or thiosemicarbazones even if some exceptions are known.[124]

However, for the preparation of derivatives which contain a functional group directly attached to position 6, the application of the foregoing cyclization method is considerably limited by the availability or existence of the required derivatives of α-keto acids and may also be affected by differences in their reactivity. Cyclization of thiosemicarbazones was, therefore, used for these substances only in the case of the 6-carboxylic acid[57,58] (see also Section II,B,2,a). Of the other derivatives known, the 6-acetic acid ester[62] should be mentioned. Recently some further derivatives of dioxotriazine-6-carboxylic acid were reported.[119a]

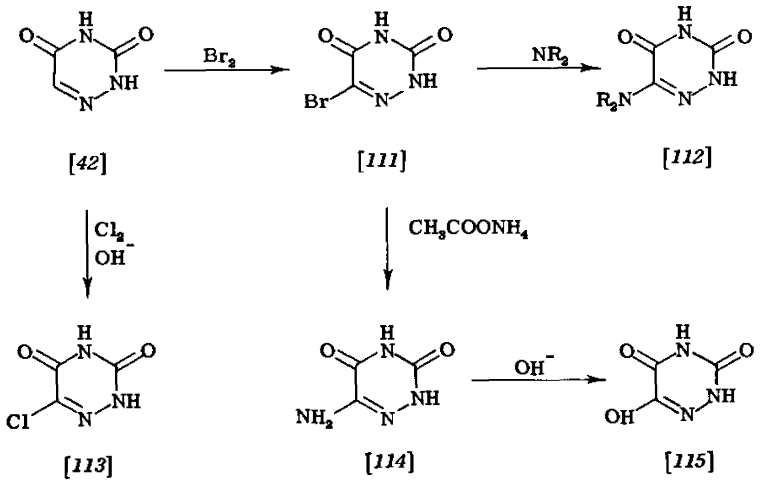
Other derivatives of this type were studied by Chang and Ulbricht[49] and were prepared by direct substitution or other secondary reactions.

Direct bromination readily yields the 6-bromo derivative (**111**), just as with uracil. Analogous chlorination and iodination requires the presence of alkalies and even then proceeds in low yield. The 6-chloro derivative (**113**) was also obtained by partial hydrolysis of the postulated 3,5,6-trichloro-1,2,4-triazine (e.g., Section II,B,6). The 6-bromo derivative(5-bromo-6-azauracil) served as the starting substance for several other derivatives.[125] It was converted to the amino derivative (**114**) by ammonium acetate which, by means of sodium nitrite in hydrochloric acid, yielded a mixture of 6-chloro and 6-hydroxy derivatives. A modified Schiemann reaction was not suitable for preparing the 6-fluoro derivative. The 6-hydroxy derivative (**115**) (an isomer of cyanuric acid and the most acidic substance of this group, $pK_a = 2.95$) was more conveniently prepared by alkaline hydrolysis of the 6-amino derivative. Further the bromo derivative was reacted with ethanolamine to prepare the 6-(2-hydroxyethyl) derivative; however, this could not be converted to the corresponding 2-chloroethyl derivative.[126] Similarly, the dimethylamino, morpholino, and hydrazino derivatives were prepared from the 6-bromo compound.[127]

In other experiments, variously substituted 6-mercapto dioxotriazines were prepared from 6-bromodioxotriazine (**111**) either by direct reaction with mercaptans or by alkylation of a mercapto derivative prepared via isothiouronium salt.[127] From these mercapto compounds alkylsufones and sulfonamido derivatives were prepared.[127a]

It may be said in conclusion that the reactivity of position 5 (i.e., 6 of the triazine ring) is similar to that of uracil. The only difference seems to be in the failure to prepare 5-nitro-6-azauracil although this reaction proceeds readily with uracil.

[124] F. Adickes, *Ber. deut. chem. Ges.* **58**, 211 (1925).
[125] P. K. Chang, *J. Org. Chem.* **26**, 1118 (1961).
[126] P. K. Chang, private communication (1961).
[127] C. Cristescu and J. Marcus, *Pharmazie* **16**, 135 (1961).



6. *3,5-Disubstituted Derivatives of 1,2,4-Triazine*

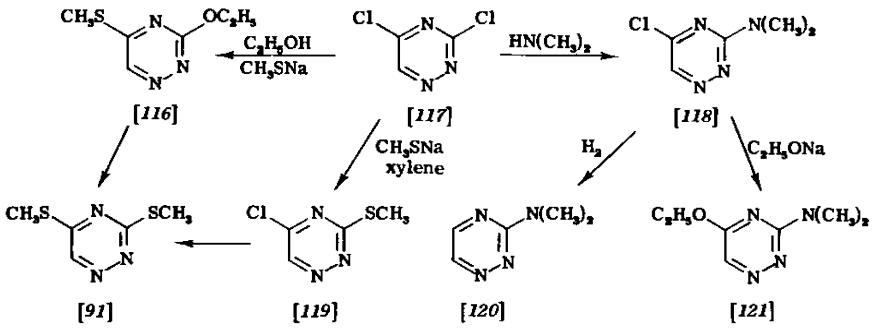
These derivatives of asymmetric triazine are rather distantly related to the group of substances reviewed here. Only those of them which are prepared from the dioxo or dithioxo derivatives will be mentioned.

On reaction with "aged" phosphoroxychloride, 6-azauracil formed 3,5-dichlorotriazine (**117**) in only a 10% yield.[40] A somewhat higher yield (30%) was obtained from the reaction of 6-bromodioxotriazine which gave 3,5,6-trichloro-1,2,4-triazine.[49,125] Similar reactions take place much more readily with uracil and in better yield.[128,129] Thus,

[127a] C. Cristescu and T. Panaitescu, *Pharmazie* **17**, 209 (1962).
[128] G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 1152 (1930).
[129] G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.* **56**, 134 (1934).

these reactions represent another difference in the reactivities of uracil and 6-azauracil.

Several other derivatives were prepared from dichlorotriazine according to Scheme 5, among these was also dimethylmercaptotriazine, later prepared in a different way. The position of the substituent is not defined in these cases.[40]



SCHEME 5

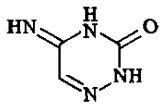
3,5,6-Trichloro-1,2,4-triazine was reacted with menthanol and subsequently crystallized from water to yield 5-chloro-6-azauracil.[49,125] A chloro-dimethoxy derivative appears to be an intermediate product, this being further cleaved by hydrogen chloride. No 2,4-dimethoxy derivatives have been prepared so far.

The thio analogs of the substances just mentioned, the alkylmercapto derivatives, are more stable and readily available (e.g., Section II,B,4,b). These derivatives were used for the preparation of the 3-hydrazino and 3,5-dihydrazino derivatives.[113]

The preparation of 3,5-diamino derivatives from 3,5-dithioxotriazines or from 6-methyl-3,5-dimethylmercapto-1,2,4-triazine was also described.[116]

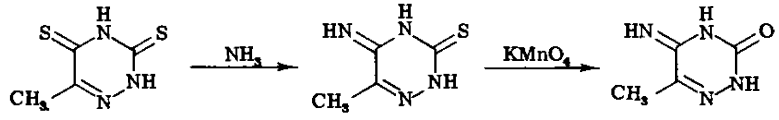
7. *3-Oxo-5-imino-2,3,4,5-tetrahydro-1,2,4-triazine (6-Azacytosine)*

Substances of this type were not studied by the earlier workers, and the first representative of this group to be investigated was 3-oxo-5-imino-2,3,4,5-tetrahydro-1,2,4-triazine (**122**) which should bear the name 6-azacytosine. It was prepared by Falco *et al.*[58] by treating 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (**88**) with alcoholic ammonia. Some *N*-substituted derivatived were prepared analogously.[119a]



[122]

The analogous 6-methyl derivative (**126**) was prepared by the same authors from 6-methyl-3,6-dithioxo derivative (**123**) as the corresponding monothioxo derivative is not easily available. Even here the substitution with ammonia took place selectively in position 4 (**124**) and the remaining sulfur atom was replaced with oxygen by oxidation with alkaline potassium permanganate (**125**).[58] A similar procedure is protected by a patent.[116]



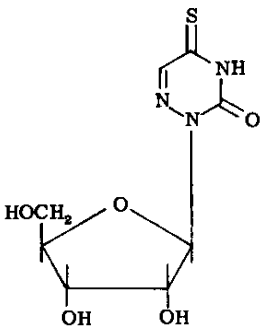
[123] [124] [125]

In contrast with cytosine, its aza analog readily undergoes hydrolysis both in acid and in alkaline solution. At 100°C hydrolysis is 50% complete within 10 min in a solution of hydrochloric acid or potassium hydroxide. The 5-methyl derivative is hydrolyzed even more readily.[58]

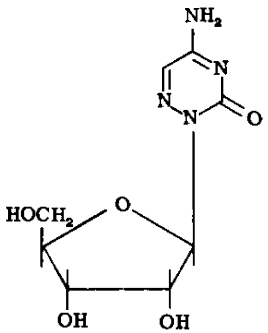
Sorm *et al.*[115] prepared azacytidine and some of its derivatives in a similar way. The 4-thio derivative was obtained from 2′,3′,5′-tri-*O*-acetyl- or 2′,3′,5′-tri-*O*-benzoyl-6-azauridine by treatment with phosphorus pentasulfide; this liberated 4-thio-6-azauridine (**126**) which was identified with 4-thio-6-azauracil on comparing the UV spectra. Treatment with ammonia produced 6-azacytidine (**127**); treatment with hydrazine, hydroxylamine, and *n*-butylamine yielded the corresponding derivatives.

The UV spectra of azacytidine are similar to those of uridine and 6-azauridine but differ from those of cytosine and cytidine. On the other hand, the spectrum of the 4-dimethylamino derivative is different from that of 6-azacytidine and similar to that of cytidine.[130]

[130] J. Žemlička, J. Beránek, and J. Smrt, *Collection Czechoslov. Chem. Communs.* **27**, 2784 (1962), and J. Žemlička, private communication (1962).



[126]



[127]

The IR spectra of chloroform solutions of 6-azacytidine and its derivatives show that these compounds, like the corresponding cytidine derivatives, exist in the amino form.[131]

Preparation of 6-azacytidine-5′-phosphate by direct phosphorylation with cyanoethylphosphate was not successful. The substance could be prepared, however, on ammonia treatment of 4-thio-6-azauridine-5′-phosphate which was obtained by phosphorylation of 2′,3′-isopropyliden-4-thio-6-azauridine with pyrophosphoryl chloride. From morpholidate of 6-azacytidine-5′-phosphate, 6-azacytidine-5′-diphosphate was prepared by the action of phosphoric acid.[132]

A new synthesis of 6-azacytidine was reported recently. Treatment of 6-azauridine tribenzoate with dimethylchlormethylammonium chloride gave the 4-chloro derivative. Reaction with ammonia and removal of the protecting groups yielded 6-azacytidine.[133]

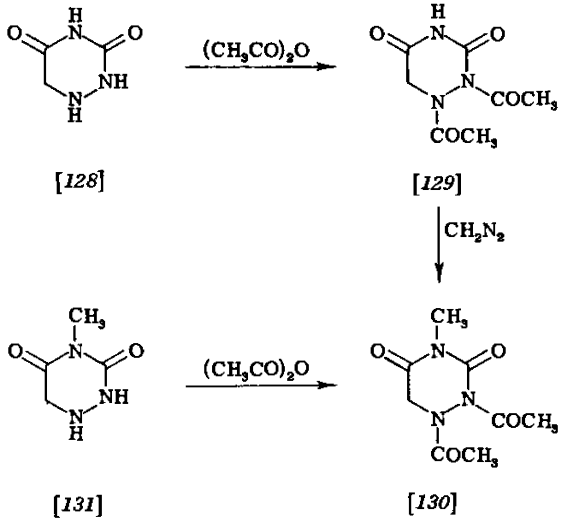
8. *Hexahydro Derivatives*

The synthesis of some 3,5-dioxohexahydro-1,2,4-triazines was described earlier (e.g., Section II,B,2,a). Other 6-substituted derivatives were prepared in the same way.[134]

[131] J. Pitha and J. Beránek, *Collection Czechoslov. Chem. Communs.*, in press.
[132] J. Beránek and F. Šorm, *Collection Czechoslov. Chem. Communs.*, in press.
[133] J. Žemlička, J. Smrt, and F. Šorm, *Tetrahedron Letters* p. 379 (1962).
[134] J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," Vol. 10 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), p. 75. Interscience, New York, 1956.

Oxidation of the hexahydro to tetrahydro derivatives was mentioned in connection with the synthesis of 3,5-dioxo-1,2,4-triazines (e.g., Section II,B,2,a). The reverse procedure, hydrogenation of the tetrahydro derivatives, was used with 6-azauracil, 6-azathymine, and their *N*-methyl derivatives. With all these compounds hydrogenation proceeds smoothly in the presence of Adams' catalyst. Only the hydrogenation of 1-methyl-6-azathymine was not successful.[65]

3,5-Dioxohexahydro-1,2,4-triazine (dihydro-6-azauracil) (**128**) yields a diacetyl derivative (**129**) which is relatively stable toward hydrolysis. The acetylation of the *N*-methyl derivatives and the course of the reaction with diazomethane indicates that acetylation takes place here in positions 1 and 2.[123]

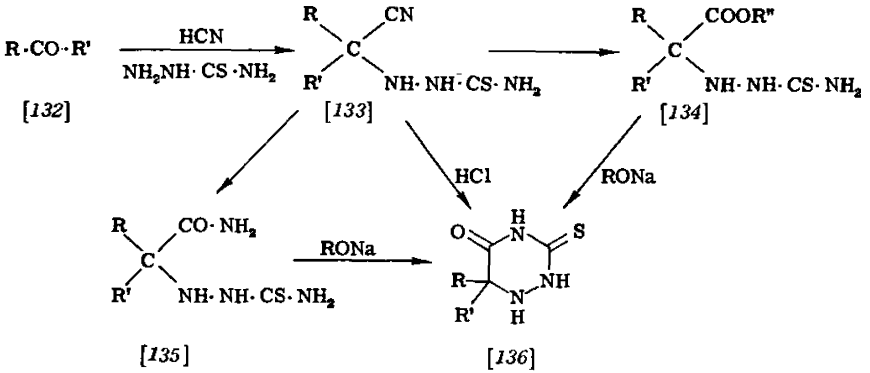


[128] [129] [131] [130]

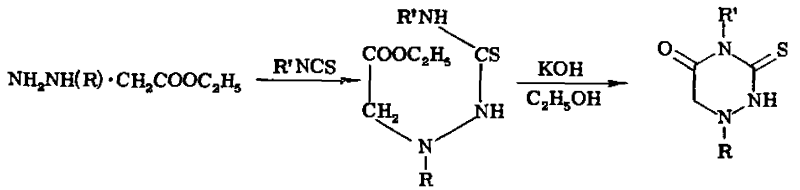
The hexahydro derivatives are much less acid than the tetrahydro ones ($pK_a > 10$).[21] Their UV spectra naturally lack the characteristic maxima.[66] The IR spectra, however, possess similar absorption to the tetrahydro derivatives in the carbonyl region.[67] It can thus be concluded that they also possess the dilactam structure.

Just as for the dioxohexahydro derivatives, substituted 3-thioxo-5-oxohexahydro-1,2,4-triazines were recently prepared by cyclization

of thiosemicarbazidoacetates.[135–137] The starting thiosemicarbazidoacetic acids (**133–135, 138**) were prepared either by simultaneous addition of hydrogen cyanide and thiosemicarbazide to ketones (**132**)[135,136] or by the reaction of hydrazinoacetates (**137**) with isothiocyanates.[137,138] The esters (**134, 138**) or amides (**135**) of thiosemicarbazido-



acetic acids thus formed were cyclized by alkaline alcoholate or hydroxide in ethanol (**136, 139**).[135,137] The nitrile of thiosemicarbazidoacetic acid (**133**) was also cyclized by concentrated hydrochloric acid.[136] Spectra of these substances (**139**) were studied by Tišler.[137]



He found that the UV maximum exhibits a hypsochromic shift in an alkaline medium. In the IR spectra he found maxima in the carbonyl

[135] R. Fusco and S. Rossi, *Gazz. chim. ital.* **84**, 373 (1954).
[136] S. R. Safir, J. J. Hlavka, and J. H. Williams, *J. Org. Chem.* **18**, 106 (1953).
[137] M. Tišler, *Vestnik Sloven. kemi. društva* **7**, 69 (1960).
[138] M. Busch and E. Meussdörffer, *Ber. deut. chem. Ges.* **40**, 1021 (1907).

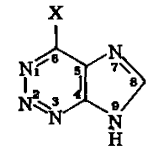
group regions but no maximum was present for a SH group. Hence he concludes that these substances possess the thiolactam form.

III. Aza Analogs of Purine Bases

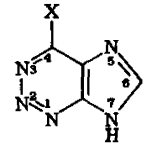
A. 2-Aza Analogs

1. *Nomenclature*

The names of 2-aza analogs are derived by formal substitution of the methine group in the 2-position of the purine skeleton by a nitrogen atom (**140**). Since this position is substituted in some purine bases, only the aza analogs of adenine or hypoxanthine are amenable to such formal derivation.



[140]



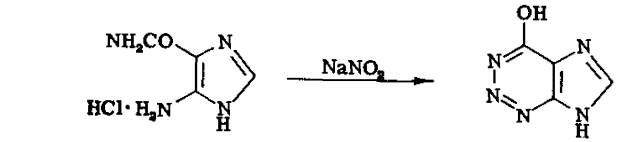
[141]

The systematic nomenclature used originally the term imidazo-1,2,3-triazine. The *Chemical Abstracts* indexes use the more accurate name imidazo[4,5-*d*]-*v*-triazine (**141**). The numbering of the substituents is different in the two systems of nomenclature as may be seen in the formulas.

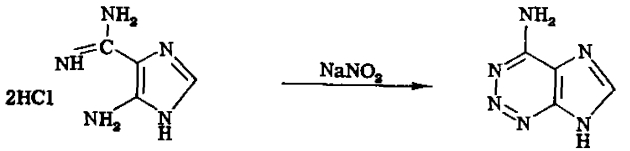
2. *Preparation and Properties*

Substances of this type have hitherto received little attention. One of the reasons appears to be the limited possibilities of preparation. The only known method of preparation, described by Woolley *et al.*,[139] proceeds from the derivatives of 4-aminoimidazole-5-carboxylic acid. The amide of this acid (**142**) is treated with nitrous acid to yield 4-hydroxyimidazo[4,5-*d*]-*v*-triazine (2-azahypoxanthine) (**143**), the amidine (**144**) yielding the 4-amino derivative (2-azaadenine) (**145**) under the same conditions. 2-Azahypoxanthine was probably obtained in the same way earlier but was not identified.[139]

[139] D. W. Woolley, E. Shaw, N. Smith, and E. A. Singer, *J. Biol. Chem.* **189**, 401 (1951).



[142] [143]



[144] [145]

When it was found later that enzymatic oxidation of 2-azaadenine yields its 8-hydroxy derivative (4-amino-6-hydroxyimidazo[4,5-*d*]-*v*-triazine), its synthesis was also achieved by the procedure already described.[140]

Very few data exist on the physicochemical properties of these substances. The stability of 2-azaadenine against hydrolysis with hot hydrochloric acid and on the formation of silver salts have been mentioned; furthermore, their UV spectra have been published without detailed interpretation.[139,140]

B. 8-Aza Analogs

1. *Nomenclature*

The 8-aza analogs are formally derived by substitution of the methine group in position 8 of the purine ring. The names thus derived preserve the numbering of the purine ring (**146**), and are frequently used in papers of biochemical character, but in chemical papers only along with systematic names.

[146] [147]

[140] E. Shaw and D. W. Woolley, *J. Biol. Chem.* **194**, 641 (1952).

According to the systematic nomenclature these substances were first named 1-*v*-triazolo[*d*]pyrimidines in compliance with the general principles of the Ring Index.[141] More recent papers and *Chemical Abstracts* indexes use the term *v*-triazolo[4,5-*d*]pyrimidine (**147**) in accord with the IUPAC nomenclature. The numbering of substituents when using the last-mentioned name is different from that of the 8-aza analogs. For the formulas of oxygen and sulfur derivatives names derived from the lactim or thiolactim form are almost exclusively in use (in common with the purine derivatives). These derivatives are thus described as hydroxy and mercapto derivatives, respectively. The name 1,2,3,4,6-pentaazaindene is used only rarely for this system.

2. *Methods of Preparation*

The 8-aza analogs of purine bases were the first to be studied among all the aza analogs of nucleic acid bases (as early as 1945). Before that time the chemistry of these substances had not been treated in detail from any aspect. Thus the entire chemistry of the *v*-triazolo [4,5-*d*]pyrimidines was developed only in connection with the study of antimetabolites of nucleic acid components. Therefore all the papers involved are largely of preparative character and only rarely discuss theoretical points.

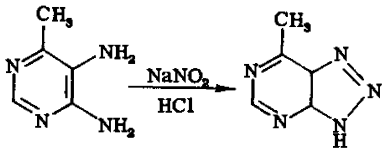
For the preparation of triazolopyrimidines three main types of synthesis are in use. The first of these proceeds from a pyrimidine derivative (especially the 4,5-diamino derivatives) and closes the triazole ring. The second method proceeds, on the contrary, from derivatives of *v*-triazole to close the pyrimidine ring. The third method finally is one which yields the derivatives through substitution or replacement of substituents in compounds prepared by one of the first-named procedures.

a. From Purine Derivatives. The only older work published on these substances is the paper by Gabriel and Colman[142] who treated 6-methyl-4,5-diaminopyrimidine (**148**) with nitrous acid and obtained a product which they designated as "4,5,6-methylazimidopyrimidine" (**149**); it appears, however, that a compound of this type was prepared even before that by Traube[143] who called it "azimid" (**150**).

[141] R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.* **67**, 290 (1945).

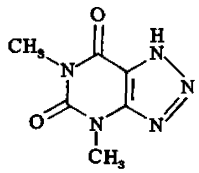
[142] S. Gabriel and J. Colman, *Ber. deut. chem. Ges.* **34**, 1234 (1901).

[143] W. Traube, *Ber. deut. chem. Ges.* **33**, 3035 (1900).



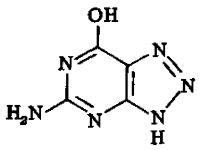
[148]

[149]



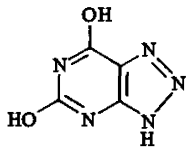
[150]

This synthetic procedure was used without any significant changes for the preparation of the greatest number of derivatives of *v*-triazolo[4,5-*d*]pyrimidine. Roblin *et al.*[141] prepared the aza analogs of the principal purine bases: 8-azaguanine (**151**), 8-azaadenine (**152**), 8-azaxanthine (**153**), and 8-azahypoxanthine (**154**). By similar methods,



[151]

[152]



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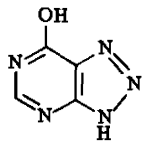


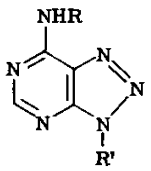
[154]

labeled 8-azaadenine[144] and 8-azaguanine were prepared.[144,145] A number of other derivatives can be grouped under the several structural types. There are 9-substituted or disubstituted derivatives of 8-

[144] E. L. Bennett, *J. Am. Chem. Soc.* **74**, 2420 (1952).
[145] H. G. Mandel, E. L. Alpen, W. D. Winters, and P. K. Smith, *J. Biol. Chem.* **193**, 63 (1951).

azaadenine (**155**),[146-150] 9-substituted or disubstituted derivatives of 8-azaguanine (**156**)[151-155] and 9-substituted derivatives of 8-azaxanthine (**157**),[153] 8-azahypoxanthine (**158**),[149,155a] and 2,6-diamino-8-azapurine (**159**).[153,154] Further derivatives have been prepared in which one or both functional groups in positions 2 and 6 are modified[148,156-162] and a variety of mixed types.[148,151,163-167] A similar procedure was used for the preparation of the glycityl derivatives of 8-azaguanine in which the D-ribityl or D-sorbityl residue was unequivocally bound in position 3 of the triazolopyrimidine ring (i.e., analogous to position 9 of the natural purine nucleosides) (**156**; R = H, R′ = ribityl or sorbityl).[168,169]

[146] J. H. Lister and G. M. Timmis, *J. Chem. Soc.* p. 327 (1960).
[147] R. Hull, *J. Chem. Soc.* p. 2746 (1958).
[148] R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.* **25**, 765 (1960).
[149] C. L. Leese and G. M. Timmis, *J. Chem. Soc.* p. 4107 (1958).
[150] L. Almirante, *Ann. chim. (Rome)* **49**, 333 (1959); *Chem. Abstr.* **53**, 20078 (1959).
[151] S. Yamada, I. Chibata, and D. Kiguchi, *Tanabe Seiyaku Kenkyû Nempô* **2**, 13 (1957); *Chem. Abstr.* **52**, 1177 (1958).
[152] M. J. Fahrenbach, K. H. Collins, M. E. Hultquist, and J. M. Smith, Jr., *J. Am. Chem. Soc.* **76**, 4006 (1954).
[153] H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.* **81**, 3046 (1959).
[154] G. M. Timmis, D. G. I. Felton, H. O. J. Collier, and P. L. Huskinson, *J. Pharm. and Pharmacol.* **9**, 46 (1957); *Chem. Abstr.* **51**, 10531 (1957).
[155] S. Yamada and I. Chibata, Jap. patent 6338 (1958); *Chem. Abstr.* **54**, 2375 (1960).
[155a] C. Temple, R. L. McKee, and J. A. Montgomery, *J. Org. Chem.* **27**, 1671 (1962).
[156] Cilag Ltd., British patent 674,594 (1952); German patent 836,802 (1952); *Chem. Abstr.* **47**, 7553 (1953).
[157] D. S. Acker and J. E. Castle, *J. Org. Chem.* **23**, 2010 (1958).
[158] F. F. King and T. J. King, *J. Chem. Soc.* p. 943 (1947).
[159] P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta* **34**, 835 (1951).
[160] F. L. Rose, *J. Chem. Soc.* p. 3448 (1952).
[161] C. T. Bahner and D. E. Bilancio, *J. Am. Chem. Soc.* **75**, 6038 (1953).
[162] K. L. Dille and B. E. Christensen, *J. Am. Chem. Soc.* **76**, 5087 (1954).
[163] R. Hull, *J. Chem. Soc.* p. 481 (1959).
[164] K. L. Dille, M. L. Sutherland, and B. E. Christensen, *J. Org. Chem.* **20**, 171 (1955).
[165] L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.* **70**, 3875 (1948).
[166] J. H. Lister, *J. Chem. Soc.* p. 3394 (1960).
[167] F. L. Rose, *J. Chem. Soc.* p. 4116 (1954).
[168] J. Davoll and D. D. Evans, *J. Chem. Soc.* p. 5041 (1960).
[169] D. L. Ross, C. G. Skinner, and W. Shive, *J. Org. Chem.* **26**, 3582 (1961).



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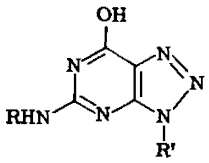
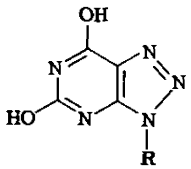
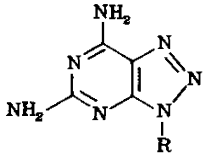


[156]



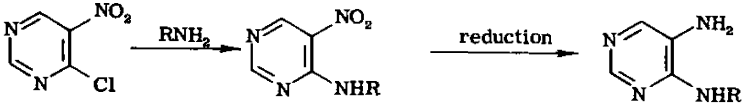
[157]

[158]



[159]

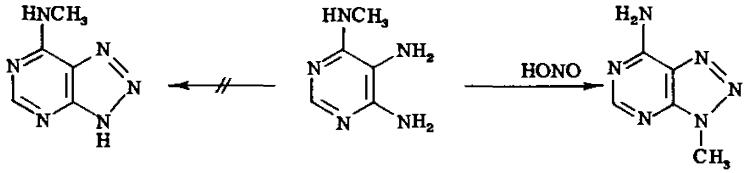
The general applicability of this synthesis follows from the great number of compounds prepared. The preparation of derivatives substituted in the pyrimidine ring and in position 3 of the triazolopyrimidine ring is principally determined by the possibility of preparing the suitably substituted derivatives of 4,5-diaminopyrimidines which represent the common starting substances. Through these starting compounds the preparation of 8-azapurines is closely related to the preparation of analogous purines which can also be prepared from 4,5-diaminopyrimidines by the action of formic acid or its derivatives. The amino group can be introduced into position 4 of the pyrimidine ring by substitution of the analogous 4-chloro derivatives[163-165] (**160**). In this manner *N*-substituted 4-amino derivatives (**162**) afford unequivocally 3-substituted triazolopyrimidines on reacting with nitrous acid. The 1-substituted derivatives would be accessible only with



[160] [161] [162]

difficulty by this method. The amino group in position 5 of the starting 4,5-diaminopyrimidines is usually prepared by the reduction of the readily available 5-nitro derivatives[150,162,164,165] (**161**). It follows

from the nature of the cyclization by nitrous acid that it is impossible to prepare 2-substituted and 1,3-disubstituted derivatives. It is known that the secondary amino group enters the cyclization more readily than does the primary one.[149] This is also borne out by the result of cyclization of 4,5-diamino-6-methylaminopyrimidine (**164**) which led to 3-methyl-7-amino-*v*-triazolo[4,5-*d*]pyrimidine (**165**) rather than to the 7-methylamino derivative[148] (**163**).



[163] [164] [165]

The mechanism of cyclization of diaminopyrimidines by nitrous acid appears not to have been studied in detail. For the preparative procedure an aqueous solution of alkaline nitrite is treated with the diaminopyrimidine either in the form of a salt or with simultaneous addition of hydrochloric or acetic acid. The first phase of the reaction is usually carried out at 0°C, in some cases the reaction being terminated by heating to 50–60°C. With diaminopyrimidines which are sparingly soluble in water, the reaction was carried out in an organic solvent using amylnitrite.[154,159] Excess nitrous acid can possibly attack the amino groups present. This was employed in some cases for the preparation of the hydroxy derivatives.[170,171]

Another synthesis of *v*-triazolo[4,5-*d*]pyrimidines described first by Benson *et al.*[172] and by Hartzel and Benson[173] also involves closing the triazole ring. It proceeds from a derivative of 4-aminopyrimidine (**166**), and making use of the aromatic character of the 5-position in the pyrimidine nucleus produces 4-amino-5-arylazo derivatives (**167**) by coupling with benzenediazonium chloride. These derivatives under-

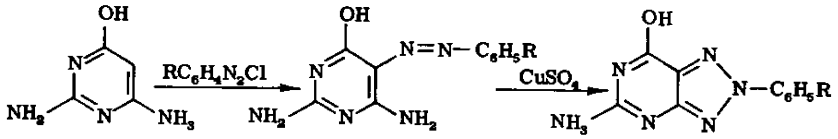
[170] F. Bergmann, G. Levin, and H. Kwietny, *Arch. Biochem. Biophys.* **80**, 318 (1959).

[171] R. P. Parker and J. S. Webb, U.S. Patent 2,543,333 (1951); *Chem. Abstr.* **45**, 7605 (1951).

[172] F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Am. Chem. Soc.* **72**, 1816 (1950).

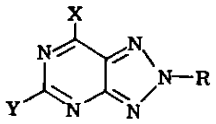
[173] L. W. Hartzel and F. R. Benson, *J. Am. Chem. Soc.* **76**, 2263 (1954).

go oxidative cyclization by cupric sulfate in pyridine to triazolopyrimidine derivatives (**168**). This synthesis is thus suitable for



[*166*] [*167*] [*168*]

derivatives with aromatic residues in position 2. As concerns substitution in the pyrimidine nucleus, the situation here is the same as for the preceding synthesis. In this way it was possible to prepare a larger number of derivatives of type (**169**), where X and Y = H, alkyl, amino, hydroxy, mercapto, or alkylmercapto group and R = substituted phenyl or 3-pyridyl.[154,171-174]



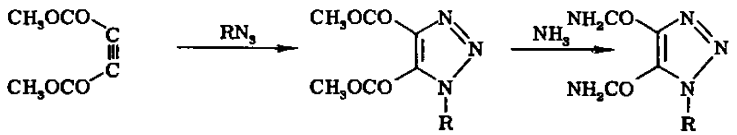
[*169*]

b. From Triazole Derivatives. Syntheses proceeding from triazole derivatives represent to a certain extent an analogy with syntheses of the purine derivatives. Their variability is considerably lower than for the preceding syntheses and their application has therefore been limited.

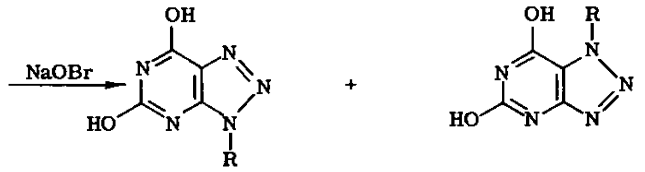
The first method was used by Baddiley *et al.*[175,176] for the synthesis of glycosyl derivatives of *v*-triazolo[4,5-*d*]-pyrimidines. Proceeding from acetylenedicarboxylic acid ester (**170**) and a glycosyl azide (R = tetra-*O*-acetyl-β-D-glucopyranosyl, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl, or 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl), they prepared the diester (**171**) and further the diamide of substituted triazoledicarboxylic acid (**172**). Using a procedure developed for analogous

[174] I. Ježo and Z. Votický, *Chem. zvesti* **6**, 357 (1952); *Chem. Abstr.* **48**, 7019 (1954).
[175] J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.* p. 1651 (1958).
[176] J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.* p. 3606 (1958).

purine derivatives,[177] a Hoffmann reaction (action of alkaline hypobromite) gave a mixture of the corresponding esters of 1- and 3-glycosyl-5,7-dihydro-*v*-triazolo[4,5-*d*]-pyrimidines (**173**, **174**).



[*170*] [*171*] [*172*]



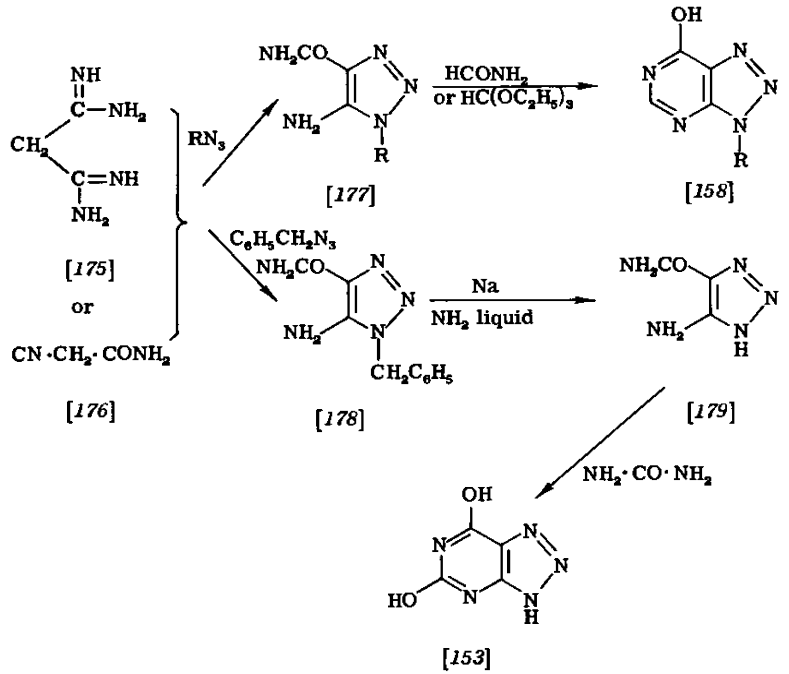
[*173*] [*174*]

This synthesis is thus suitable preparing 5,7-dihydroxy derivatives (substituted 8-azaxanthines). However, with regard to the 1- or 3-substituted derivatives its course is not unequivocal.

The second procedure of this type was first described by Yamada *et al.*[178] They used the diamidine of malonic acid (**175**) or cyanacetamide (**176**) to prepare 1-benzyl-5-amino-*v*-triazole-4-carboxamide (**178**) by treatment with benzyl azide. After removing the benzyl group with sodium in liquid ammonia they converted the product (**179**) by heating with urea to 5,7-dihydroxy-*v*-triazolo[4,5-*d*]pyrimidine (8-azaxanthine) (**153**).

A similar procedure was developed in greater detail by Dornow and Helberg.[179] They proceeded from aryl or aralkyl azid and cyanacetamide (**176**) and the 1-aryl- or 1-aralkyl-5-amino-*v*-triazole-4-carboxamide (**177**) formed was then cyclized with formamide or ethyl orthoformate. In this way they prepared 3-substituted 7-

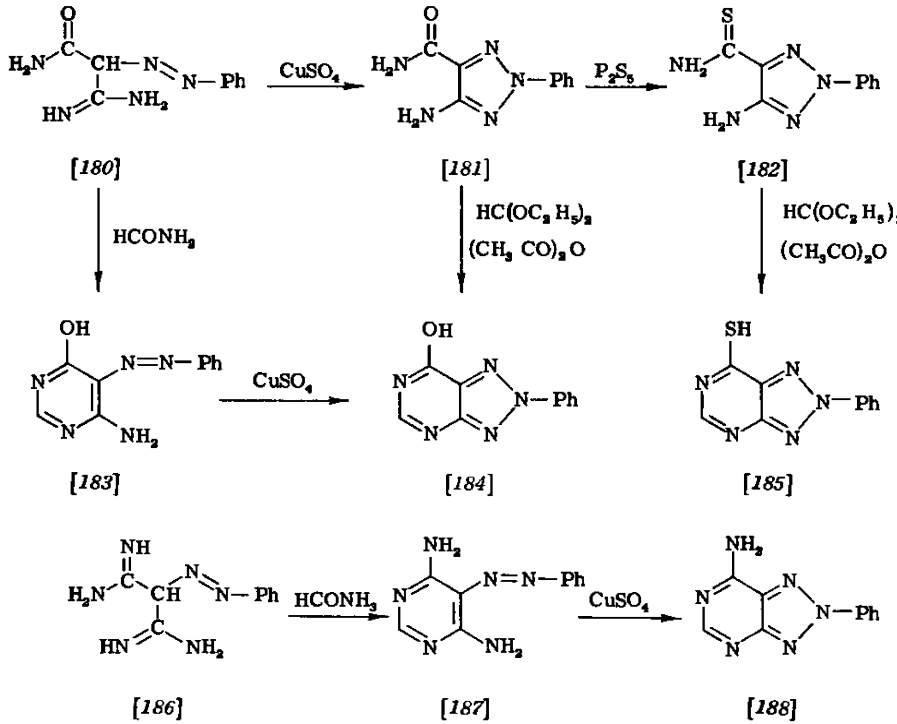
[177] R. A. Baxter and F. S. Spring, *J. Chem. Soc.* p. 378 (1947).
[178] S. Yamada, T. Mizoguchi, and A. Ayata, *Yakugaku Zasshi* **77**, 455 (1957); *Chem. Abstr.* **51**, 14698 (1957).
[179] A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).



hydroxy-*v*-triazolo[4,5-*d*]-pyrimidines (9-substituted 8-azahypoxanthines) (**158**) in which R = phenyl, *p*-chlorophenyl, *m*-chlorophenyl, *m*-nitrophenyl, and benzyl. These examples also point to the possibility of application of this synthesis.

A combination of the preceding type of synthesis and of cyclization of 4-amino-5-arylazopyrimidine can be seen in the novel procedure of Richter and Taylor.[180] Proceeding from phenylazomalonamide-amidine hydrochloride (**180**), they actually close both rings in this synthesis. The pyrimidine ring (**183**) is closed by formamide, the triazole (**181**) one by oxidative cyclization in the presence of cupric sulfate. Both possible sequences of cyclization were used. The synthetic possibilities of this procedure follow from the combination of the two parts. The synthesis was used for 7-substituted 2-phenyl-1,2,3-triazolo[4,5-*d*]-pyrimidines (**184, 185**). An analogous procedure was employed to prepare the 7-amino derivatives (**188**) from phenylazomalondiamidine (**186**).

[180] E. Richter and E. C. Taylor, *J. Am. Chem. Soc.* **78**, 5848 (1956).



c. By Substitution. The last method of preparation of triazolopyrimidines is the exchange of substituents or direct substitution in derivatives prepared by one of the previously described paths. During these reactions on the pyrimidine ring of the molecule, a similar course can be expected as in the corresponding pyrimidine and purine derivatives. The differences in reactivity do not appear to have been studied in detail but they can be seen from the abundant material available, i.e., derivatives prepared by substitution of the amino group of 8-azaguanine,[181-183] in some cases, ensued for preparation of the soluble derivatives.[181] Further mention should be made of the replacement

[181] K. Abe, S. Onishi, Y. Koriki, and K. Matsui, Jap. patent 9984, (1958); *Chem. Abstr.* **54**, 5713 (1960).

[182] K. Abe, S. Onishi, Y. Kunugi, and K. Matsui, *Tanabe Seiyaku Kenkyû Nempô* **2**(2), 11 (1957).

[183] Cilag Ltd., Swiss patent 279,102 (1952); *Chem. Abstr.* **47**, 8097 (1953).

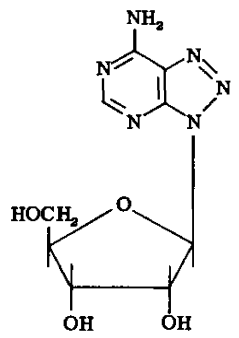
of the hydroxyl group by mercapto through the action of phosphorus pentasulfide,[184-187] conversion of the mercapto group[170] to hydroxy or amino[148] and the already mentioned replacement of amino by a hydroxy group through treatment with nitrous acid.[170,171] More attention has been devoted to the preparation of derivatives by nucleophilic substitution of the chlorine atom in position 7.[188] Preparative modification of all these reactions is analogous to the corresponding reactions in the purine and pyrimidine series.

More interesting are the substitution reactions on the triazole ring where a characteristically different course can be expected from that of analogous reactions in the purine series. These reactions were studied in more detail only in connection with the preparation of the glycosyl derivatives, and the experimental material does not permit the drawing of general conclusions.

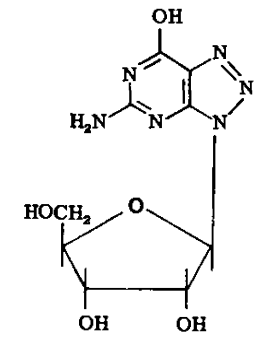
The process of glycosidization of mercuric or chloromercuric salts used with purine bases was applied by Davoll[189] to their 8-aza analogs. He obtained two isomeric glucosyl derivatives from the 7-acetamino derivative, one of the products being identical with unequivocally prepared 3-glucosyl derivative (through cyclization with nitrous acid). An analogous reaction yielded only one ribosyl derivative to which the structure of the 3-ribofuranosyl derivative (8-azaadenosine) (**189**) was ascribed on the basis of UV spectra similarity. 5,7-Diamino-*v*-triazolo[4,5-*d*]pyrimidine yielded a ribosyl derivative which possessed a different UV spectrum from that of the 3-substituted derivatives. The 7-amino-5-mercaptomethyl derivative yielded a mixture of two ribosyl derivatives, one of which was converted in two stages to a riboside identical with 8-azaguanosine (**190**) obtained enzymatically.

Andrews and Barber[190] described the reaction of tri-*O*-benzoyl ribofuranosyl chloride with the chloromercuric salt of 7-dimethylamino-5-

[184] C. T. Bahner, D. E. Bilancio, E. B. Senter, S. Humphries, R. Nations, W. Porch, and J. Wilson, *J. Org. Chem.* **22**, 558 (1957).
[185] Wellcome Found., Ltd., British patent 765,590 (1957); *Chem. Abstr.* **51**, 12157 (1957).
[186] C. T. Bahner, D. E. Bilancio, and E. M. Brown, *J. Am. Chem. Soc.* **76**, 1370 (1954).
[187] C. T. Bahner, B. Stump, and M. E. Brown, *J. Am. Chem. Soc.* **75**, 6301 (1953).
[188] Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.* **26**, 4433 (1961).
[189] J. Davoll, *J. Chem. Soc.* p. 1593 (1958).
[190] K. J. M. Andrews and W. E. Barber, *J. Chem. Soc.* p. 2768 (1958).



[*189*]



[*190*]

methylmercapto-*v*-triazolo[4,5,*d*]-pyrimidine. The position of the ribofuranosyl group cannot be considered as established, however.

Angier and Marsico[191] followed the course of alkylation first. The 7-dimethylamino-5-methylmercapto derivative reacted with dimethyl sulfate in an alkaline medium to yield a mixture of the 2- and 3-methyl derivatives. The reaction of the 7-dimethylamino derivative with ethyl iodide in an alkaline medium led to a mixture of all three possible monoethyl derivatives. The position of the alkyl group in all these substances was defined by comparing the UV spectra with derivatives prepared by a straightforward synthesis. After reacting the mercuric salts with tri-*O*-benzoylribofuranosyl chloride, they demonstrated the ribose residue to be bound in position 2. The same structure was shown to be valid for the derivative prepared by Andrews and Barber.[190]

It can be concluded on the basis of the present material that the course of substitution is affected both by substituents in the nucleus and by the character of the substituent to be introduced. No general rules can be formulated at present, however.

Similarly, the position of the acyl group in derivatives formed by the reaction with acetic hydride or benzoyl chloride[192] and the position of the carboxymethyl group in the derivative formed by the reaction with chloracetic acid are not established.[193]

[191] R. B. Angier and J. W. Marsico, *J. Org. Chem.* **25**, 759 (1960).
[192] F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.* **76**, 2798 (1954).
[193] N. Sugimoto and S. Imado, Jap. patent 1372 (1958); *Chem. Abstr.* **53**, 1389 (1959).

To the derivatives prepared on substitution belong also the nucleotides of 8-azaguanosine (**190**). From the 5′-phosphate, prepared enzymatically, the corresponding diphosphate and triphosphate were synthesized by the action of *N,N′*-dicyclohexylcarbodiimide and phosphoric acid.[194] From 2′,3′-*O*-isopropylidene-8-azaguanosine and 2-cyanoethyl dihydrogen phosphate, the 8-azaguanosine-5′-phosphate (8-azaguanylic acid)[195] resulted which was identical with the product obtained enzymatically.[196] The 2′,3′-phosphate and 2,3′-cyclic phosphate were prepared from the 5′-trityl derivative of 8-azaguanosine.[196a]

For the preparation of some of the triazolopyrimidine derivatives enzymatic reactions were also used. Thus, for example, the preparation of deoxyribofuranosyl-[197] and ribofuranosyl-8-azaguanine (8-azaguanosine)[197,198] was described. On the basis of the assumed specific course of the enzyme reactions these substances are considered to have the structure of 3-glycosyl derivatives (corresponding to position 9 of natural purine nucleosides). No chemical or physicochemical proof of the structure has been presented so far. Enzymatic deamidation of 8-azaguanine to 8-azaxanthine was also described.[199–201] 8-Azaguanosine-5′-phosphate[196] and -triphosphate[194] were also prepared enzymatically.

3. *Properties*

Triazolopyrimidines and their derivatives are relatively stable toward alkaline and acid hydrolysis. However, the action of aqueous sodium hydroxide, ammonia, or hydrazine under pressure converts them to derivatives of 1,2,3-triazole.[202,203]

[191] J. L. Way, J. L. Dahl, and R. E. Parks, Jr., *J. Biol. Chem.* **234**, 1241 (1959).
[195] J. A. Montgomery and H. J. Thomas, *J. Org. Chem.* **26**, 1926 (1961).
[196] J. L. Way and R. E. Parks, Jr., *J. Biol. Chem.* **231**, 467 (1958).
[196a] H. J. Thomas, K. Hewson, and J. A. Montgomery, *J. Org. Chem.* **27**, 192 (1962).
[197] M. Fredkin, *J. Biol. Chem.* **209**, 295 (1954).
[198] J. Kára, J. Škoda, and F. Šorm, *Collection Czechoslov. Chem. Communs.*, **26**, 1386 (1961).
[199] A. Roush and E. R. Norris, *Arch. Biochem.* **29**, 124 (1950).
[200] E. Hirschberg, J. Kream, and A. Gellhorn, *Cancer Research* **12**, 524 (1952).
[201] J. Kream and E. Chargraff, *J. Am. Chem. Soc.* **74**, 4274 (1952).
[202] J. S. Webb and A. S. Tomcufcik, U.S. patent 2,714,110 (1955); *Chem. Abstr.* **50**, 12116 (1956).
[203] S. Yamada, T. Mizoguchi, and A. Ayata: *Yakugaku Zasshi* **77**, 441 (1957); *Chem. Abstr.* **51**, 12107 (1957).

The UV spectra were measured for practically all the numerous derivatives. Beside the analytical application of these to demonstrate the position of the substituent[191] no detailed interpretation was attempted, however. On the whole, they are similar to the spectra of analogous purine derivatives and also display a similar dependence on pH.[141,146,165] Despite the fact that the question of structure with regard to the lactim–lactam (or thiolactim–thiolactam) tautomerism has not been studied in detail, it can be assumed that oxygen and sulfur derivatives, at variance with the conventional way of writing the formulas, possess a lactam or thiolactam structure.[188] This is in agreement with the views on the analogous purine derivatives.

Among the other physicochemical studies mention should be made of the determination of the electron structure and energy of resonance[204,205] carried out for a number of the principal 8-aza analogs, and of the determination of the dissociation constants[206] and crystal structure.[207,208]

[204] A. Pullman, B. Pullman, and G. Berthier, *Compt. rend. acad. sci.* **243**, 380 (1956).
[205] B. Pullman and A. Pullman, *Bull. soc. chim. France*, **7**, 973 (1958).
[206] Y. Hirata, I. Teshima, and T. Goto, *Nagoya Sangyô Kagaku Kenkyûjo Kenkyû Hôkoku No. 9*, p. 80 (1956); *Chem. Abstr.* **51**, 8516 (1957).
[207] W. Nowacki and H. Bürki. *Experientia* **7**, 454 (1951).
[208] W. Nowacki and H. Bürki, *Z. Elektrochem.* **56**, 788 (1952).

Quinazolines

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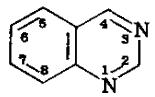
I. Introduction

Quinazoline (1,3-diazanaphthalene) was prepared by Gabriel[1] in 1903 although the first derivative was synthesized by Griess 34 years earlier.[2] The name was proposed by Widdege.[3] Other names such as phenmiazine, benzo-1,3-diazine, and 5,6-benzopyrimidine have occasionally been used. The numbering suggested by Paal and Busch[4] (**1**) is still in use.[5]



[*1*]

[1] S. Gabriel, *Ber. deut. chem. Ges.* **36**, 800 (1903).
[2] P. Greiss, *Ber. deut. chem. Ges.* **2**, 415 (1869).
[3] A. Widdege, *J. prakt. Chem.* **36** (2), 141 (1887).
[4] C. Paal and M. Busch, *Ber. deut. chem. Ges.* **22**, 2683 (1889).
[5] I. U. P. A. C., "Nomenclature of Organic Chemistry" -B-2.11, p. 57. Butterworths, London, 1957; Ring Index RRI 1626.

The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected in the reactions of quinazoline. The properties of substituted quinazolines depend largely on (a) the nature of the substituents, (b) whether they are in the pyrimidine ring or in the benzene ring, and (c) whether or not complete conjugation is present in the pyrimidine ring.

The reader is referred to previous reviews[6,7] for historical aspects and early work. For condensed quinazoline systems, "The Chemistry of Heterocyclic Compounds—Six Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings"[8] should be consulted.

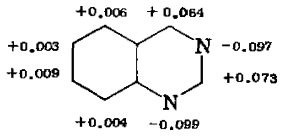
The present review describes recent advances in quinazoline chemistry, some of which are but modern applications of earlier methods, whereas others strike out on new, and sometimes surprising, pathways. The structure of the cation of the parent substance, quinazoline, has only recently been made clear, and it has become evident that covalent hydration is a phenomenon widely distributed throughout the quinazoline series. With this fact in mind, it seems better to set forth the newly found properties of quinazolines before proceeding to an account of advances in synthesis.

II. Properties of Quinazoline

A. Physical Properties

1. *Electron Density Diagram*

Theoretical treatment by Brown[9] has led to the electron density



[2]

[6] T. A. Williamson, "Heterocyclic Compounds" (R. C. Elderfield, ed.), Chap. 8. Wiley, New York, 1957.
[7] J. K. Landquist, "Chemistry of Carbon Compounds. IVB, Heterocyclic Compounds" (E. H. Rodd, ed.), Chap. XV. Elsevier, Amsterdam, 1959.
[8] C. F. H. Allen, "The Chemistry of Heterocyclic Compounds—Six Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings." Interscience, New York, 1951.
[9] R. D. Brown, private communication, Monash University, Melbourne (1961).

diagram (2) for quinazoline. These values were obtained by molecular orbital calculations using uniform parameters. They are self-consistent and give dipole moments in agreement with experiment.

2. *Structure of the Quinazoline Cation*

Unlike the other diazanaphthalenes (i.e., naphthyridines,[10] cinnoline,[11] phthalazine,[12] and quinoxaline), quinazoline shows abnormal behavior when converted into its cation. This anomaly was first discovered by Albert *et al.*,[13] who noticed that 4-methylquinazoline was a weaker base (tenfold) than quinazoline (see Table I). This was

TABLE I
Ionization of Quinazolines

Compound	pK_a	Compound	pK_a
Quinazoline	3.51	4-Methylquinazoline	2.52
2-Methylquinazoline	4.52	2,4-Dimethylquinazoline	3.60

unexpected because a methyl group is normally base strengthening. A study of the ultraviolet spectra of the neutral molecule[14] and cation of quinazoline and 4-methylquinazoline revealed that the cation of the former was anomalous. The diazanaphthalenes, not unlike naphthalene, show three main bands in the ultraviolet spectra and these are only slightly altered on protonation. The quinazoline anomaly consists of a marked hypsochromic shift (45 mμ) on protonation (see Fig. 1). The neutral molecule is not anomalous because it shows the typical three bands and its spectra in water and cyclohexane[15] are essentially similar. The spectra of the neutral molecule and cation of 4-methylquinazoline are very similar (see Fig. 2). The cation of quinazoline in water, therefore, has a different electronic system, and the hydrated amidinium structure (3) was postulated for it.[11,16,17]

[10] A. Albert, *J. Chem. Soc.* p. 1790 (1960).
[11] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.* p. 4191 (1956).
[12] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* p. 2689 (1961).
[13] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.* p. 3832 (1954).
[14] Neutral molecule in this and future reference indicates the unprotonated species which is the species present in solution in nonpolar solvent, and in water 2 pH units (or more) above the pK_a value.
[15] M. Claesen and H. Vanderhaeghe, *Bull. soc. chim. belges*, **66**, 276 (1957).
[16] A. Albert, *Chem. Soc.* (*London*) Spec. Publ. No. 3, p. 138 (1955).
[17] A. Albert, "Heterocyclic Chemistry," p. 121. Athlone Press, London, 1959.

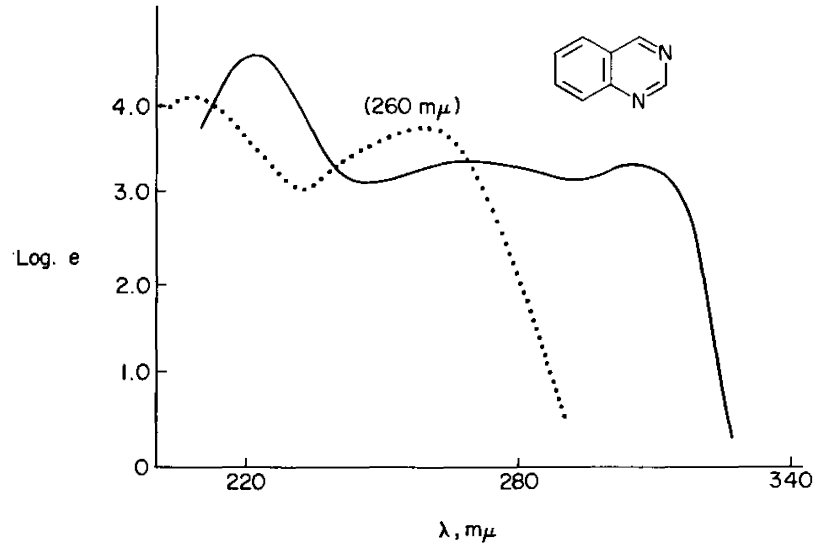


FIG. 1. Ultraviolet spectrum of quinazoline in water. Solid line, neutral molecule; dotted line, cation.

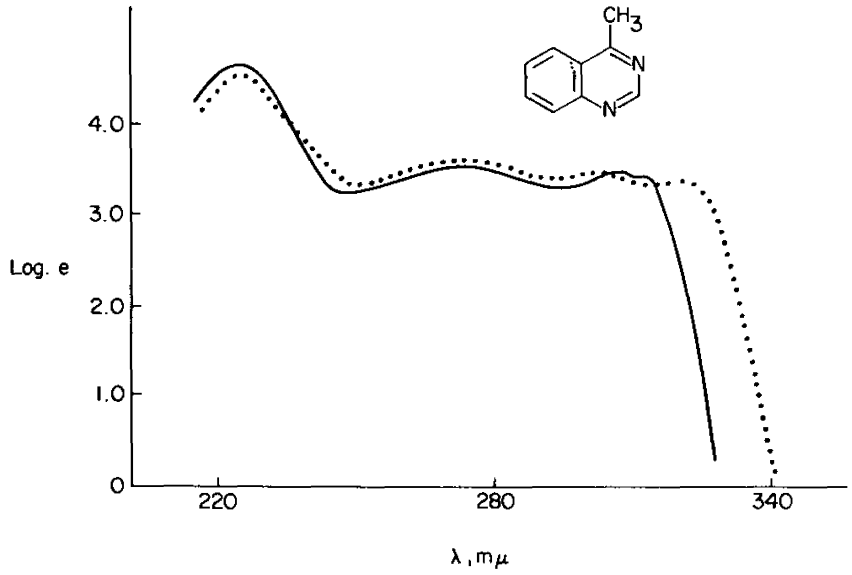
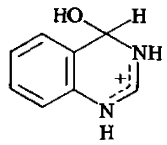


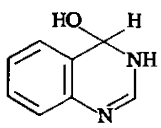
FIG. 2. Ultraviolet spectrum of 4-methylquinazoline in water. Solid line, neutral molecule; dotted line, cation.



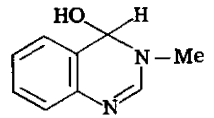
[3]

The hydrochloride of (3) holds water rather tenaciously,[12] and the infrared spectrum indicates that the water is covalently bound. Mild oxidation of the cation (3) gives 4-hydroxyquinazoline in high yield and ring-chain tautomerism is excluded on the grounds that quinazoline does not give a positive aldehyde test in acid solution. 2-Methylquinazoline also has an anomalous cationic spectrum and a high basic strength (see Table I), but 2,4-dimethylquinazoline is normal in both these respects, which supports the view that abnormal cation formation entails attack on an unsubstituted 4-position.[12]

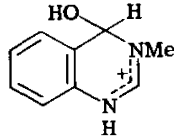
The stabilizing influence in the hydrated cation is the amidinium resonance. If a solution of the cation is neutralized, a short-lived hydrated neutral molecule (4) (half-life 9 sec at pH 10) is obtained with an ultraviolet spectrum similar to that of the hydrated cation but shifted to longer wavelengths (5 mμ).[18] Supporting evidence can be derived from the anhydrous nature of the cation of 4-nitroisoquinoline (pK_a 1.35),[19] in which the nitro group has a similar electronic influence to that of the ring nitrogen atom N-1 in quinazoline and where amidinium resonance is not possible.



[4]



[5]



[6]

The structure of the unstable hydrated neutral molecule (4) was deduced from the similarity of its ultraviolet spectrum with that of the "pseudo base" (5), derived from (6) of known structure. This

[18] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* p. 5267 (1961).
[19] A. Bryson, *J. Am. Chem Soc.* **82**, 4871 (1960).

carbinolamine (5) has no carbonyl band in the infrared spectrum (solid and solution), and its ultraviolet spectrum in cyclohexane and in water are the same, thus eliminating ring-chain tautomerism in this case also. The similarity of (4) and (5) is paralleled by (3) and (6) and proves the postulated structure (3) of the hydrated quinazoline cation conclusively.[18]

3. *Hydration Pattern in Substituted Quinazolines*

As yet no quinazoline has been discovered which has any appreciable amount (say, 1%) of hydrated species in the neutral molecule,[20] but several quinazolines were shown to contain a mixture of anhydrous and hydrated species in the cations.[21] Anhydrous neutral molecules and anhydrous cations have an ultraviolet absorption spectrum of the general type C (Fig. 3) and hydrated cations, the type

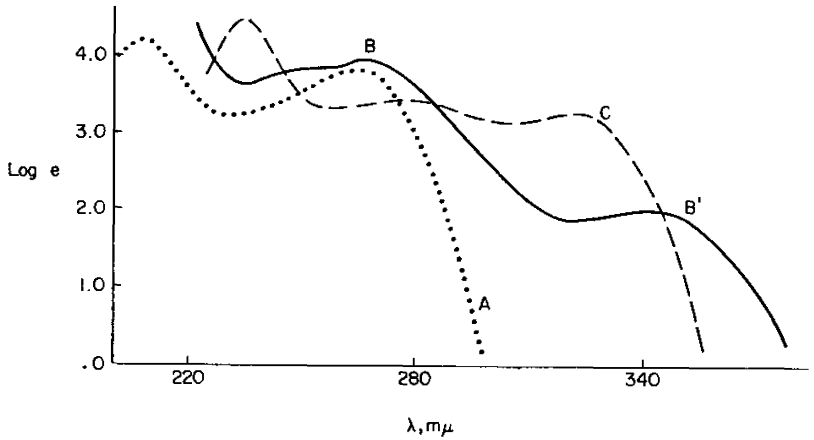


FIG. 3. Ultraviolet spectra of quinazoline cations in water. A, Typical hydrated cation; B B′, typical mixture of hydrated and anhydrous cation, and C, typical anhydrous cation.

A. Cations, on the other hand, which are a mixture of hydrated and anhydrous species have an intermediate spectrum of the type B B′. The long-wavelength absorption band B′ is due to the anhydrous cation, and the short-wavelength absorption band B to the hydrated

[20] The existence of the equilibria described in Section II,A,4 implies the presence of at least a very small amount of hydrated neutral species.
[21] W. L. F. Armarego, *J. Chem. Soc.* p. 561 (1962).

cation. The intensities of these bands depend on the relative amount of the species present, and the absorption of the long-wavelength band has been used to obtain a rough estimate of the percentage of anhydrous species in the mixture. The estimated percentages are in agreement with those derived from kinetic data (see Section II,A,5). The nature and position of substituents have a marked effect on the nature of the cations and these are shown in Table II. The dehydrating influence on the cation due to a substituent in position 4 (where OH attack occurs), and also in position 7 (*para* to position 4) when the latter is substituted with a group that has a strong $+T$ effect, is of particular interest.[21]

TABLE II
PERCENTAGE OF ANHYDROUS CATION IN THE MIXTURE OF ANHYDROUS AND HYDRATED CATIONS OF SUBSTITUTED QUINAZOLINES

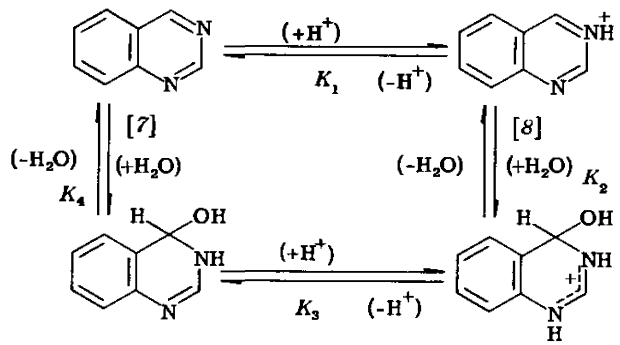
Quinazoline	%	Method	Quinazoline	%	Method
Unsubstituted	A	s,k	5-Methoxy	B–B′	s,k
2-Methyl	A	s,k	6-Methoxy	B–B′	s,k
4-Methyl	C	k	7-Methoxy	C	s,k
2,4-Dimethyl	C	k	8-Methoxy	A	s,k
5-Methyl	B–B′	s,k	5-Hydroxy	B–B′	s
6-Methyl	B–B′	s,k	6-Hydroxy	B–B′	s
7-Methyl	B–B′	s,k	7-Hydroxy	C	s
8-Methyl	B–B′	s,k	8-Hydroxy	B–B′	s
5-Chloro	A	s	5-Amino	B–B′	s
6-Chloro	A	s,k	6-Amino	A	s
7-Chloro	A	s,k	7-Amino	C	s
6,8-Dichloro	A	s,k	8-Amino	B–B′	s

Notation: A, 0%; B–B′, 4–25%; C, 75–80%; s, from long-wavelength band intensities; k, from rate of dehydration.

4. *Significance of Ionization Constants*

The ionization constant of a typical heterocyclic compound (e.g., quinoline) designates the equilibrium involving a proton, a neutral molecule and its cation. With quinazoline, however, two distinct species (hydrated and anhydrous) are involved each of which is in equilibrium with its cation, and can be represented as in the reaction scheme, (7), (8), (3), and (4).

The pK_a value of 3.51, determined by potentiometric titration,



represents an over-all and composite ionization constant involving the equilibria K_1, K_2, K_3, and K_4. This is simplified in quinazoline itself because the amount of (4) in equilibrium with (7) in the neutral molecule, and (8) in equilibrium with (3) in the cation, is very small. No hysteresis has been observed in the titrations hence the equilibria are established rapidly. The pK_a value for the equilibrium K_1 was predicted to be ~1.5 but that for the equilibrium K_3 was found to be 7.77. The latter constant was determined spectrophotometrically by immediately mixing an acid solution of (3) with various buffers and measuring the initial (extrapolated) optical density of (4).[22] The hydration–dehydration process is acid–base catalyzed.

Although the dehydration of (4) to (7) is rapid, the initial ultraviolet absorption could be obtained accurately by extrapolation and the ionization constant determined. This is because the pK_a value (7.77) is in a pH region where hydrogen ion catalysis is small. In contrast the pK_a value for the equilibrium K_1 is low and in a region where the process (8) → (3) is strongly catalyzed by hydrogen ions—it is too rapid for measurement by the foregoing technique. The ionization constants for equilibria such as K_1 will, therefore, have to wait for the application of faster measuring techniques.

As a rough guide, the larger the ratio of hydrated to anhydrous species in either the neutral molecule *or* in the cation, the higher will

[22] This technique was developed for these systems in this Department by Dr. D. D. Perrin who first demonstrated the presence of the hydrated neutral species (4).

be the over-all pK_a. This pK_a also depends on the ionization constants of the anhydrous and of the hydrated species in addition to the ratios mentioned. Substituents which have a marked effect on the cationic spectrum of quinazoline (see Table II) also have a similar effect on the ionization constants and this is in agreement with the considerations given in the foregoing.[21,23] The over-all ionization constants for comparison purposes are of no significance, except perhaps to give some idea of the degree of hydration if either the neutral molecules or the cations are, respectively, largely anhydrous or hydrated. Such a constant is too complicated for interpretation when both the neutral molecule and cation are partially hydrated, as in pteridine.[24]

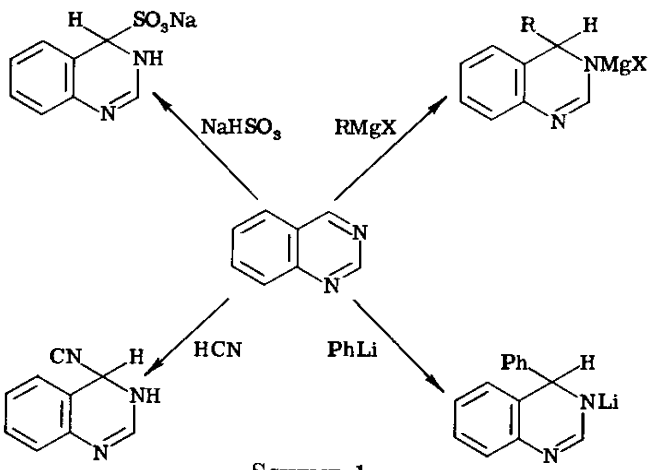
The hydrated cation of quinazoline in dilute acid solution becomes dehydrated when the acidity of the solution is progressively increased. At H_0 —4.3, the solution consists predominantly of the anhydrous cation with some anhydrous dication (~7%). The ultraviolet spectrum of the anhydrous cation is similar to that of the neutral molecule (there is a small bathochromic shift) and it is also similar to that of quinazoline in anhydrous dichloroacetic acid.[12] When the acid strength is further increased to H_0 —9.4, the quinazoline dication is formed (pK_a —5.5).

5. *Kinetics of the Hydration–Dehydration Process*

The existence of the short-lived hydrated neutral molecule (4) has been demonstrated in several benz-substituted quinazolines[21] and the over-all rate of dehydration has been determined at pH 10. This was done by neutralizing a solution containing the cation and measuring the rate of increase of optical density in the spectral region B′ (see Fig. 3) where absorption due to species (4) is negligible. The absorption at zero time (extrapolated) gives the amount of anhydrous species present in the cation, and the absorption at infinite time gives the total amount of anhydrous and hydrated species in the cation mixture. The percentages of anhydrous to hydrated species in the cations of substituted quinazolines obtained by this method are in agreement with those obtained earlier (see Table II).[21] Although the process is described as an over-all rate of dehydration, it

[23] The only exceptions are the benz-substituted nitroquinazolines which have unexpectedly high basic strengths.

[24] D. D. Perrin, *J. Chem. Soc.* p. 645 (1962).



SCHEME 1

dicates that position 4 is subject to nucleophilic attack but does not explain why position 4 is more favored than position 2. The reactivity of quinazoline toward Michael reagents (i.e., malonic ester, acetoacetic ester, cyanoacetic ester, and acetone) has been demonstrated[34] but no products have yet been isolated.

The sole known example of *electrophilic* substitution in quinazoline is nitration. Quinazoline gives 6-nitroquinazoline with fuming nitric acid in concentrated sulfuric acid.[35] No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation (see Section II,A,4) is not present. This substitution is in agreement with theoretical calculation [see (2) and reference 36].

Reduction of quinazoline with hydriodic acid gives 3,4-dihydroquinazoline[1] but this can be achieved more satisfactorily by catalytic means.[35] With palladium-charcoal it was found possible to reduce quinazoline to 1,2,3,4-tetrahydroquinazoline.[37]

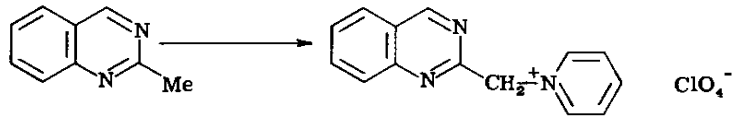
III. Properties of Substituted Quinazolines

1. *Alkyl and Arylquinazolines*

These are stable to distillation and crystallization. The substituents

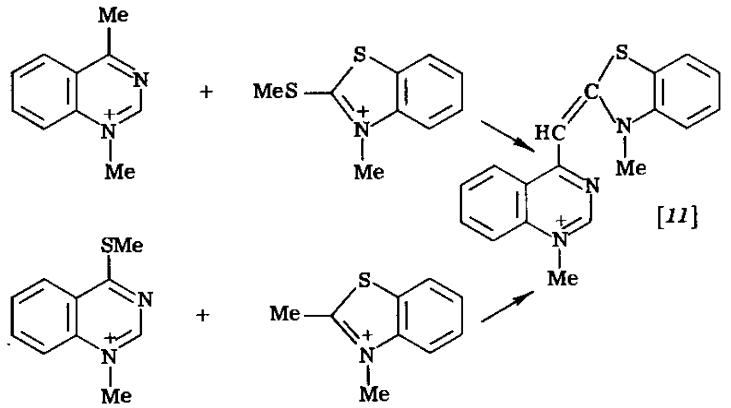
[35] R. C. Elderfield, T. A. Williamson, W. J. Gensler, and C. B. Kremer, *J. Org. Chem.* **12**, 405 (1947).
[36] M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* p. 2521 (1957).
[37] K. Adachi, *Yakugaku Zasshi* **77**, 507 (1957) (English Summary); *Chem. Abstr.* **51**, 14744 (1957).

behave in many ways as in other heterocyclic systems. Methyl groups in positions 2 and 4 are reactive and can condense with diethyl oxalate,[38] phthalic anhydride,[39] and benzaldehydes[40,41] and undergo a Mannich reaction.[42] 2-Methylquinazoline also reacts with pyridine in the presence of iodine to form the pyridinium salt (**10**) which was isolated as the perchlorate in 78% yield.[43]



[*10*]

Methylation of 2- or 4-methylquinazoline is reported to proceed with difficulty,[40] but 4-methylquinazoline has been quaternized with methyl iodide. The product was very hygroscopic and, although not purified, was shown to consist mostly of 1,4-dimethylquinazolinium iodide, since it gave the same cyanine dye (**11**) with 2-methylthiobenzthiazole metho-toluene-*p*-sulfonate as did 1-methyl-4-methylthioquinazolinium iodide (of unambiguous structure) with 2-methylbenzthiazole methiodide.[32]



[*11*]

[38] W. Borsche and W. Doeller, *Ber. deut. chem. Ges.* **76**, 1176 (1943).
[39] M. T. Bogert and M. Heidelberger, *J. Am. Chem. Soc.* **34**, 183 (1912).
[40] M. T. Bogert and H. Clark, *J. Am. Chem. Soc.* **46**, 1294 (1924).
[41] K. Adachi, *Yakugaku Zasshi* **77**, 514 (1957) (English Summary); *Chem. Abstr.* **51**, 14745 (1957).
[42] J. Siegel and B. E. Christensen, *J. Am. Chem. Soc.* **73**, 5777 (1951).
[43] W. Reid and H. Bender, *Chem. Ber.* **89**, 1893 (1956).

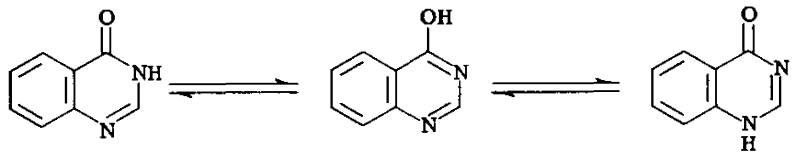
2-Alkylquinazolines are catalytically reduced to the corresponding 3,4-dihydro derivatives.[44] The only example of a 4-substituted quinazoline which was reduced to its 3,4-dihydro derivative is 2-chloro-4-phenylquinazoline which gave 4-phenyl-3,4-dihydroquinazoline.[45]

4-Methylquinazolines are susceptible to oxidation, as is shown by the attempted nitration of 2,4-dimethylquinazoline which causes the removal of the methyl group with formation of 4-hydroxy-2-methyl-6-nitroquinazoline.[46] When the 4-substituent is —C(Et)$(CO_2Et)_2$ recrystallization of the picrate from ethanol is sufficient to convert it to 4-hydroxyquinazoline.[47] Similar hydrolyses occur in acid solution and the mechanism undoubtedly involves a hydrated intermediate.[12]

2. *Hydroxyquinazolines*

These are high-melting water-insoluble substances. They are readily soluble in alkali and form stable salts.[3,4,48,49] They undergo bromination and nitration,[50] the first nitro group entering position 6 and the second, position 8; they are stable to oxidation, although severe conditions give 2,4-dihydroxyquinazolines.[30,51] Infrared spectra of 2- and 4-hydroxyquinazolines and 2,4-dihydroxyquinazoline show the presence of strong N—H and C=O stretching vibrations.[52,53] The ultraviolet spectrum of 4-hydroxyquinazoline when compared with that of 4-methoxyquinazoline, 3-methyl-4(3*H*)quinazolinone and 1-methyl-4(1*H*)quinazolinone indicates that the equilibria (**12**), (**13**), and (**14**) are present. The lactam form (**14**) is the least favored[54] and (**12**), the most favored.[55] 2-Hydroxy- and 2,4-dihydroxy-quinazolines are subject to the same tautomerism, but the spectrum of the former is more complicated because of the evidence of partial hydration in the

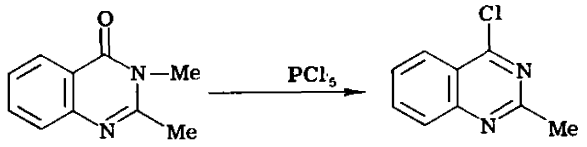
[44] W. L. F. Armarego, *J. Chem. Soc.* p. 2697 (1961).
[45] K. Schofield, *J. Chem. Soc.* p. 1927 (1952).
[46] A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.* **70**, 2423 (1948).
[47] R. C. Elderfield and I. Serlin, *J. Org. Chem.* **16**, 1669 (1951).
[48] M. Körner, *J. prakt. Chem.* [2] **36**, 155 (1887).
[49] H. G. Söderbaum and O. Widman, *Ber. deut. chem. Ges.* **22**, 1665 (1889).
[50] M. T. Bogert and G. A. Geiger, *J. Am. Chem. Soc.* **34**, 524 (1912); M. T. Bogert and G. Scatchart, *J. Am. Chem. Soc.* **41**, 2052 (1919).
[51] H. G. Söderbaum and O. Widman, *Ber. deut. chem. Ges.* **22**, 2933 (1889).
[52] H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.* **74**, 4830 (1952).
[53] S. F. Mason, *J. Chem. Soc.* p. 5874 (1957).
[54] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.* p. 3318 (1951).
[55] G. B. Barlin, private communication (1961).



[*12*] [*13*] [*14*]

neutral molecule.[56] 2-Methoxyquinazoline is undoubtedly partly hydrated.[21]

The lactam-lactim tautomerism of hydroxyquinazolines is reflected in their chemical reactivity. Thus they are chlorinated to 4-chloroquinazolines (see Section VI,A), and both *O*- and *N*-methylation have been observed. When a substituent is already present on a nitrogen atom, as in 3-methyl-4(3*H*)quinazolinone, chlorination gives 4-chloroquinazoline with loss of the methyl group[57] (see 1a). 2-



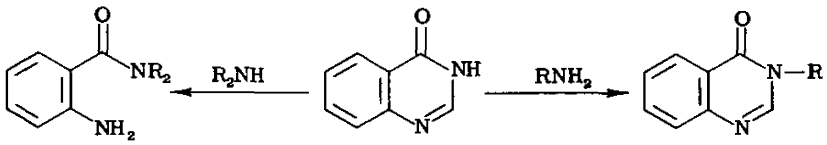
[1a]

Methyl-4-hydroxyquinazoline reacts with organic halides, in the presence of sodium methoxide, to give 3-substituted 2-methyl-4(3*H*)-quinazolinones.[57,58] The *O*-acetyl derivative of 4-hydroxyquinazoline has been prepared under anhydrous conditions and gives the hydroxy compound with water or with lithium aluminum hydride. The N-3 acetyl derivative, however, is more stable and gives 3-methyl-4(3*H*)-quinazolinone with lithium aluminum hydride.[59]

4-Hydroxyquinazolines react with primary amines or hydrazines to form 3-substituted 4(3*H*)quinazolinones (**15**).[60,61] The mechanism was shown to involve ring opening because with secondary amines (where ring closure is not possible) *N*-disubstituted benzamides are formed.

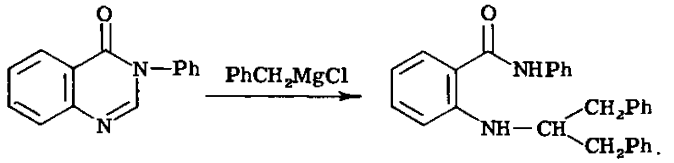
Grignard reagents do not always react in the normal way with

[56] D. D. Perrin, private communication (1961).
[57] M. T. Bogert and C. E. May, *J. Am. Chem. Soc.* **31**, 507 (1909).
[58] A. Buzas and C. Hoffman, *Bull. soc. chim. France,* **26**, 1889 (1959).
[59] R. Mirza, *Nature* **186**, 716 (1960).
[60] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.* **11**, 341 (1946).
[61] N. L. Leonard, W. V. Ruyle, and L. C. Bannister, *J. Org. Chem.* **13**, 617, 903 (1948).



[15]

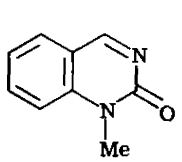
3-substituted 4(3*H*)quinazolinones, e.g., cleavage of the 2,3-bond occurs particularly when position 2 is unsubstituted[62] (see 1b).



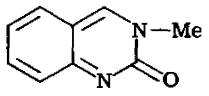
[1b]

3. *N-Methyl Derivatives*

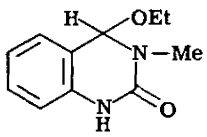
Methylation of hydroxyquinazolines invariably produces a mixture of *O*- and *N*-methylated derivatives. The *N*-methyl derivatives are, therefore, best prepared by unequivocal syntheses. 1-Methyl-2(1*H*)-quinazolinone (**16**) is not known. When *o*-aminobenzaldehyde is treated with methylisocyanate, 3-methyl-2(3*H*)quinazolinone (**17**) is obtained.[55] If this is heated in ethanol it dissolves and an alcoholate, presumably (**18**), crystallizes out, and this can be converted back to (**17**) by vacuum sublimation. Methylation of 1-methyl-4(1*H*)quinaz-



[16]



[17]

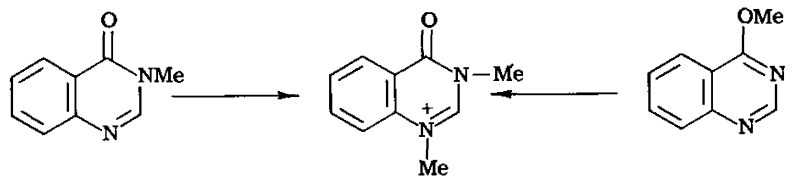


[18]

olinone, which can be prepared unambiguously from *o*-methylaminobenzamide and formic acid[3] has not been studied. Methylation of 3-methyl-4(3*H*)quinazolinone, also prepared from methyl *o*-aminobenzamide and formic acid,[63,64] gives a 1,3-dimethyl-4(3*H*)quinazoli-

[62] J. K. Kacker and I. H. Zaher, *J. Chem. Soc.* p. 415 (1956).
[63] E. Knape, *J. prakt. Chem.* [2] 43, 209 (1891).
[64] A. R. Osborn and K. Schofield, *J. Chem. Soc.* p. 3977 (1956).

none salt (**19**) and is similar to that obtained by methylation of 4-methoxyquinazoline.[32,65] Treatment of (**19**) with alkali did not give a pseudo base but gave *N*-methyl-*o*-(*N*-methylformamido)benzamide.

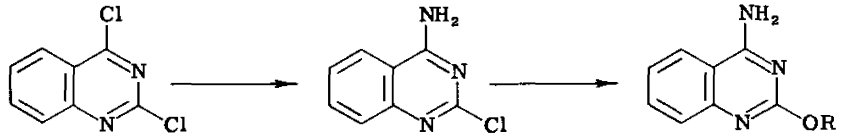


[19]

The structures of 1-methyl, 3-methyl, and 1,3-dimethyl derivatives of 2,4-dihydroxyquinazoline (which had been in doubt) have been settled.[66]

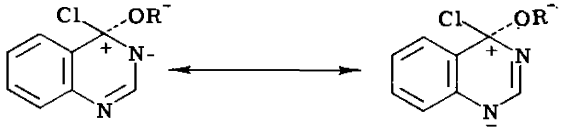
4. *Chloroquinazolines*

The halogen atom in benz-chloro substituted quinazolines is very stable (as in chlorobenzene), whereas the halogen atoms in positions 2 and 4 show the enhanced reactivity observed with halogen atoms on carbon atoms placed α and γ to heterocyclic ring nitrogens. The chlorine atom in position 4 is more reactive than in position 2,[67] and this property has been used to introduce two different substituents in the pyrimidine ring.[68]



The mechanism of hydrolysis and alcoholysis has been described,[69] and the greater reactivity of the 4-position over the 2-position is attributed to the greater stability of the transition complex (**20**) with respect to (**21**), hence its greater ease of formation.[6] The hydrolysis

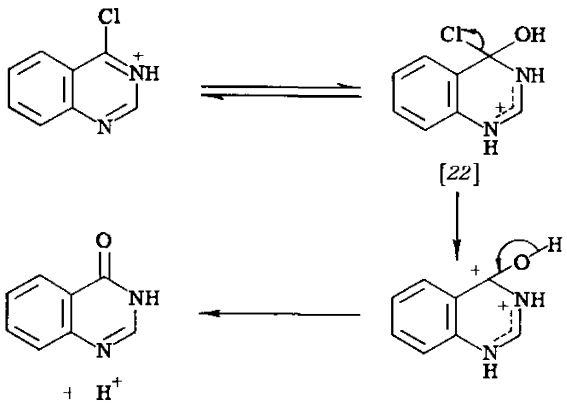
[65] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* p. 1354 (1949).
[66] C. H. Wang, T. C. Feng, and B. E. Christensen, *J. Am. Chem. Soc.* **72**, 4887 (1950).
[67] N. B. Chapman and D. Q. Russel-Hill, *J. Chem. Soc.* p. 1563 (1956).
[68] M. Claesen and H. Vanderhaeghe, *Bull. soc. chim. belges*, **68**, 220 (1959).
[69] A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.* **67**, 2112 (1945).



[20]

[21]

of these chloro compounds is autocatalyzed by the acid liberated and is much faster in the presence of acid. It probably involves a mechanism not dissimilar to the hydration in the quinazoline cation (see Section II,A) where the hydrated intermediate (**22**) prefers to lose the halogen atom rather than the hydroxyl group. There is no direct



[22]

evidence that 2- or 4-chloroquinazolines self-quaternize as does 4-chloropyridine, but the latter reacts with 4-hydroxyquinazoline under relatively mild conditions to furnish 3(4′-quinazolinyl)-4(3*H*)quinazolinone.[70]

The effect of substituents in the benzene ring on the reactivity of the halogen atom in 4-chloroquinazolines is worthy of investigation.

[70] H. Stephen and T. Stephen, *J. Chem. Soc.* p. 4178 (1956).

No doubt the reactivity parallels the hydration pattern observed in benz-substituted quinazolines (see Section II,A,3).

The versatility of pyrimidine substituted chloroquinazolines as intermediates is due to the ready replacement of the halogen atoms by hydrogen, alkyl, alkoxyl, amino, and mercapto groups (see Section VI,A).

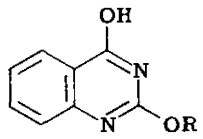
5. *Cyanoquinazolines*

The reactions of 2- and 4-cyanoquinazolines are similar to those of the chloro compounds. Thus the cyano group can be replaced by alkoxide, phenoxide, substituted amino, and hydrazino groups; substitution of the 4-cyano takes place more readily than that of the 2-cyano group.[71] The nitrile substituent can also be hydrolyzed to an alkoxycarbonyl and amide group.[72]

6. *Ethers*

Ether groups in the benzene ring of quinazoline behave as in ethers of homocyclic aromatic compounds, e.g., they can be demethylated with anhydrous aluminum chloride.[21,73] Allyl ethers also undergo a Claisen rearrangement.[74]

Ether groups in position 2 in quinazoline, although hydrolyzable can undergo nucleophilic replacement with difficulty (i.e., replacement with —NHR groups). Ether groups in position 4, on the other hand, are more like —OR groups of esters. Thus a 4-methoxy group can be quantitatively hydrolyzed to a hydroxy group with dilute acid, undergo ether exchange with alcohols,[75,76] and can be replaced



[23]

[71] T. Higashino, *Yakugaku Zasshi* **80**, 1404 (1960) (English Summary); *Chem. Abstr.* **55**, 5515 (1961).

[72] T. Higashino, *Yakugaku Zasshi* **79**, 702 (1959) (English Summary); *Chem. Abstr.* **53**, 21999 (1959); T. Higashino, *Yakugaku Zasshi* **80**, 842 (1960) (English Summary); *Chem. Abstr.* **54**, 24777 (1960).

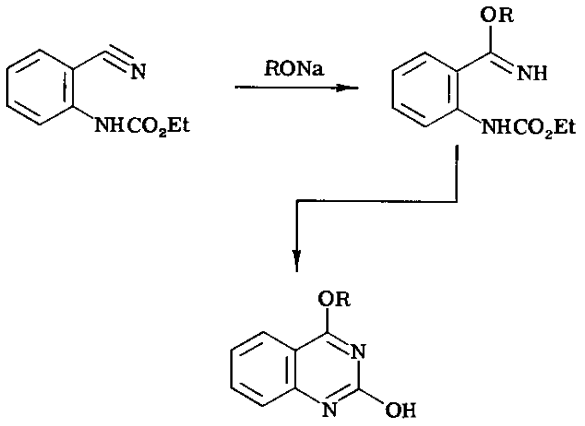
[73] A. Albert and A. Hampton, *J. Chem. Soc.* p. 4895 (1954).

[74] A. Albert and A. Hampton, *J. Chem. Soc.* p. 505 (1954).

[75] K. W. Breukink, L. H. Krol, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.* **76**, 401 (1957).

[76] N. A. Lange and F. E. Sheibley, *J. Am. Chem. Soc.* **54**, 4305 (1932).

with an amino group when heated with alcoholic ammonia in a sealed tube.[60] The latter reaction is worthy of further extension to substituted amines in view of the easy accessibility of these ethers (see Section VI,A,2).[75] Hydroxy ethers of the general formula (**23**) are made by hydrolysis of the 2,4-alkoxy diethers because of the greater reactivity of the 4-substituent, whereas ethers of the type (**24**) are most conveniently obtained by reaction of *o*-ethoxycarbonylaminobenzonitriles with excess of alkoxide.[75] The ease of replacement of

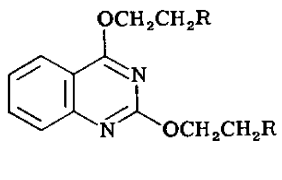


[*24*]

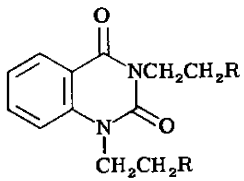
4-quinazolinyl ethers results from the higher susceptibility of the 4-position to nucleophilic attack (see Section II,B). Methylation of 2-quinazolinyl ethers has not been investigated, but 4-quinazolinyl ethers generally quaternize on N-1.[65,77]

Rearrangement of 4-quinazolinyl ethers has been known for a long time but only a few examples are recorded because the reaction is not a general one. Of the more readily rearranged ethers, 4-ethoxy-2-ethyl-6-nitroquinazoline is the most striking example, because rearrangement takes place on recrystallization from ethanol to give 2,3-diethyl-6-nitro-4(3*H*)quinazolinone.[78] Recently Grout and Partridge[79] have shown that ethers such as (**25**) (where R = NMe_2,NEt_2, or Cl) rearrange to the *N* alkylated isomers (**26**) on distillation. These workers have also shown that when R = OH the rearrange-

[77] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* p. 360 (1948).
[78] M. T. Bogert and H. A. Seil, *J. Am. Chem. Soc.* **29**, 517 (1907).
[79] R. J. Grout and M. W. Partridge, *J. Chem. Soc.* pp. 3546, 3551 (1960).

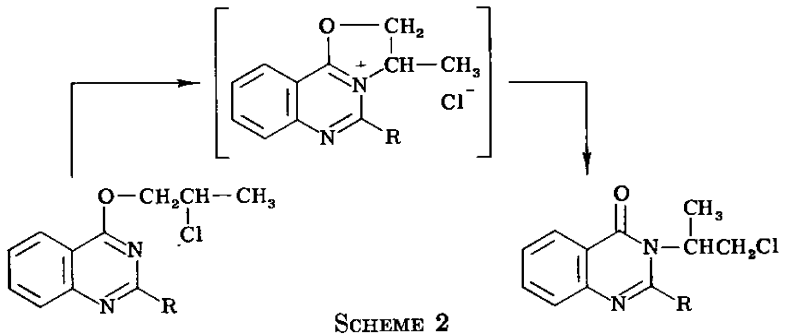


[*25*]



[*26*]

ment can be effected with thionyl chloride. A cyclic intermediate is involved in the reaction as indicated in Scheme 2 (where R = Cl but not NHPh). Attempts to rearrange allyloxy, benzyloxy, and ethoxy

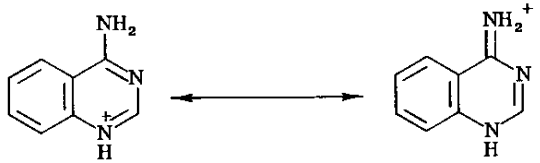


SCHEME 2

ethers were unsuccessful.

7. *Aminoquinazolines*

Amino groups in the pyrimidine ring can exist in amino and imino forms, and they show typical amino reactivity.[80] Protonation occurs on the ring nitrogen atoms[11] and the high basic strengths of the 2-, 4-, and 7-amino isomers is attributed to resonance in the cations as in (**27**). Amino groups can be replaced by hydroxy groups with

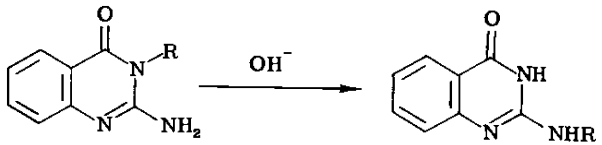


[*27*]

[80] H. J. Rodda, *J. Chem. Soc.* p. 3508 (1956).

nitrous acid.[81] The 4-amino group in particular can be replaced by a hydroxy group with concentrated hydrochloric acid.[75] 6-Aminoquinazoline undergoes a Sandmeyer reaction,[82] but it does not follow that amino groups in position 5, 7, and 8 (particularly 7) will behave in a similar manner. This is because their cations differ from that of 6-aminoquinazoline (see Table II).

The rearrangement of 1-methyl-2-aminopyrimidine to 2-methylaminopyrimidine with alkali[83] has been recently observed in aminoquinazolines.[84] The following rearrangement proceeded in high yields when R was Me, Et, Pr^n, Ph, and p-$MeOC_6H_4$:

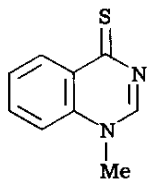


8. *Mercaptoquinazolines*

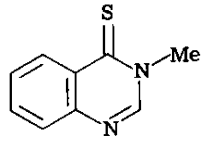
Only 2- and 4-mercapto- and 2,4-dimercaptoquinazolines are known. Like their oxygen analogs, they exhibit tautomerism. Infrared data indicates the presence of N—H and C=S stretching frequencies.[52] The mercapto group can be replaced by amino but this is more readily achieved with the corresponding methylthioethers.[60,84] Here again the 4-mercapto (and 4-methylmercapto) group is more reactive than the 2-mercapto (and 2-methylmercapto) group.[85]

Alkylation of these mercapto compounds in alkaline solution gives only the *S*-methyl derivatives.[32] Of the four isomeric *N*-methyl derivatives, the 4-thioquinazolines, (**28**) and (**29**), have been obtained from the corresponding oxo compounds with phosphorus pentasulfide[32] but the corresponding 2-thio derivatives (**30**) and (**31**) are not known. However, derivatives of substance (**31**) with methyl replaced by

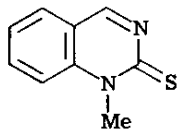
[81] E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Am. Chem. Soc.* **82**, 3152 (1960).
[82] K. Schofield and T. Swain, *J. Chem. Soc.* p. 1367 (1949).
[83] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.* p. 4035 (1955); see also H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.* p. 1858 (1955).
[84] R. J. Grout and M. W. Partridge, *J. Chem. Soc.* p. 3540 (1960).
[85] P. B. Russell, G. B. Elion, E. A. Falco, and G. H. Hitchings, *J. Am. Chem. Soc.* **71**, 2279 (1949).



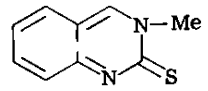
[*28*]



[*29*]

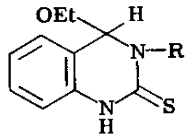


[*30*]



[*31*]

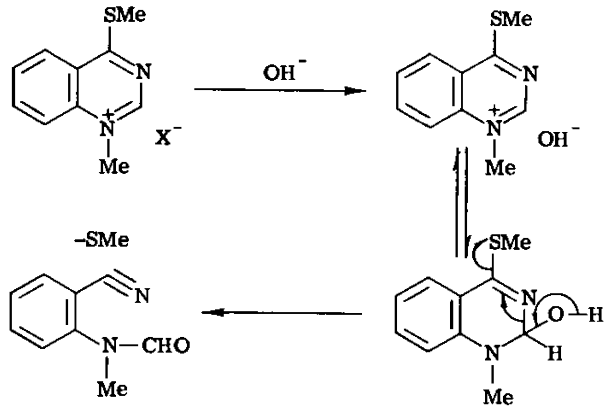
aryl groups, have been prepared[86] by reaction of aryl isothiocyanates with *o*-aminobenzaldehyde.[4] They give brilliant color reactions with acids and form hydrates and alcoholates with the general formula (**32**).



[*32*]

Methylation of 4-methylthioquinazoline occurs on N-1 since the product is the same as that obtained by methylation of 1-methyl-4(1*H*)quinazolinthione.[32] Further evidence was presented by hydrolysis with excess alkali to *o*-methylaminobenzoic acid. When only one equivalent of alkali was used *o*-methylaminobenzonitrile was formed (see Scheme 3). A similar 2,3-cleavage has also been recently observed with 6-nitro-4-methylmercaptoquinazoline.[87]

[86] C. V. Gheorghiu, *Bull. soc. chim. France* **2**, 223 (1935); L. Manolescu-Pavelescu, *Ann. Sci. Univ. Jassy* **25**, 223 (1939); see *Chem. Abstr.* **33**, 4994 (1939).
[87] E. C. Taylor, R. J. Knopf, J. A. Cagliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.* **82**, 6058 (1960).

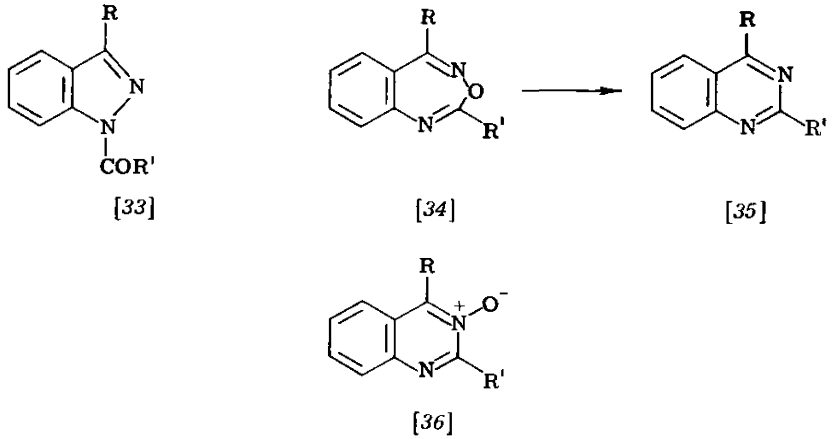


SCHEME 3

Further methylation of 2-methylmercapto- and 2,4-dimethylmercapto-quinazolines has not been studied.

IV. Quinazoline-*N*-Oxides

Quinazoline 3-oxides were first prepared by Awers and von Meyenburg[88] in 1891 by the dehydration of *o*-acylamino benzophenone oximes with acetic acid–acetic anhydride and were assigned the indazole structure (**33**). This was then modified by Bischler[89] to the

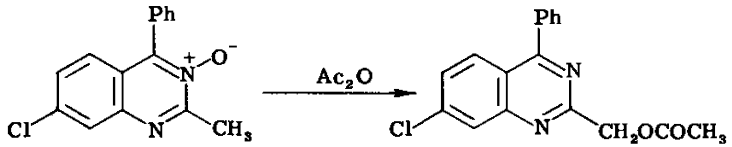


[33] [34] [35]

[36]

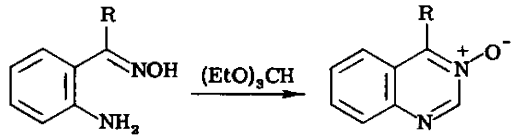
[88] K. Awers and F. von Meyenburg, *Ber. deut. chem. Ges.* **24**, 2370 (1891).
[89] A. Bischler, *Ber. deut. chem. Ges.* **26**, 1901 (1893).

oxadiazepine structure (**34**) which was later accepted by Awers.[90] Ried and Stahlhofen,[91] reduced these oxo compounds, which they also obtained by dehydration of the oximes of *o*-acylamino benzophenone and acetophenone, to 3,4-dihydroquinazolines of known structure. Reduction proceeded with absorption of two molecules of hydrogen, and these authors postulated ring opening of (**34**) followed by dehydration to (**35**) during reduction. It was not until 6 years later that Sternbach *et al.*[92] showed these structures to be quinazoline 3-oxides (**36**) on the evidence of (a) their method of preparation, (b) infrared data which show an N→O stretching frequency, (c) catalytic reduction to quinazolines, and (d) the reaction (**37**) → (**38**) with acetic anhydride which is typical of *N*-oxides.



[37] [38]

Unsubstituted *quinazoline 3-oxide* was prepared in an attempt to react quinazoline with hydroxylamine.[37] This reaction gave a product of variable composition, but when an acetone solution was heated in a sealed tube it gave quinazoline 3-oxide. The oxide is more conveniently prepared, in excellent yield, from *o*-aminobenzaldehyde oxime and ethyl orthoformate. This method appears to be of general use and has been used for the preparation of 4-methylquinazoline

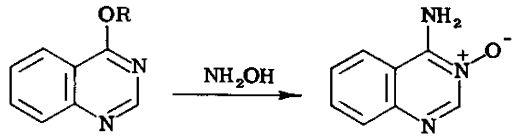


[2a]

3-oxide.[41] The reaction of quinazoline with hydroxylamine is not hindered by the presence of a 4-substituent since 4-methylquinazoline also gives 4-methylquinazoline 3-oxide with hydroxyl-

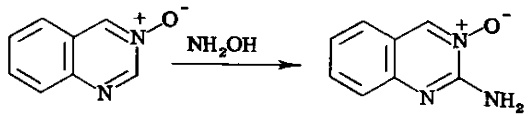
[90] K. Awers, *Ber. deut. chem. Ges.* **57**, 1723 (1924).
[91] W. Ried and P. Stahlhofen, *Chem. Ber.* **87**, 1814 (1954).
[92] L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.* **82**, 475 (1960).

amine, and 4-methoxy- and 4-phenoxy-quinazoline give 4-aminoquinazoline 3-oxide with displacement of the ether group[93] (see 2b).



[2b]

Quinazoline 3-oxide reacts further with hydroxylamine to give 2-aminoquinazoline 3-oxide (see 2c).



[2c]

These compounds show the typical reactions of heterocyclic *N*-oxides and their structure was proved by methylation which takes place on N-1. Quinazoline 3-oxide is soluble in water and melts at 155°C. It has basic properties and its pK_a value in water is 1.47.[34]

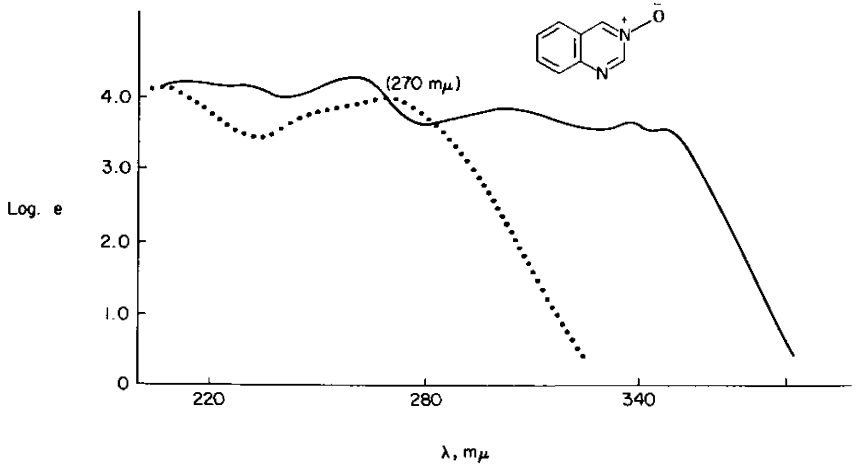
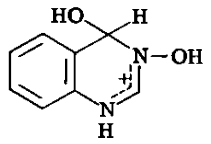


FIG. 4. Ultraviolet spectrum of quinazoline 3-oxide. Solid line, neutral molecule; dotted line, cation.

[93] K. Adachi, *Yakugaku Zasshi* **77**, 510 (1957) (English Summary); *Chem. Abstr.* **51**, 14745 (1957).

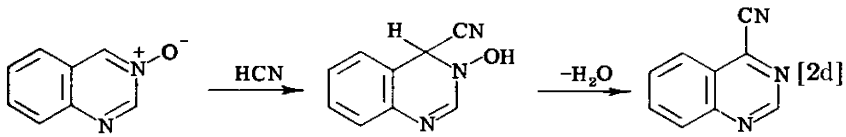
The ultraviolet spectra of the neutral molecule and the cation in water show very similar behavior to quinazoline and its cation (see Fig. 4). By analogy, the quinazoline 3-oxide cation must be co-



[39]

valently hydrated and the hydrate stabilized by an amidinium type of resonance (**39**). Furthermore 4-methylquinazoline 3-oxide is a weaker base (pK_a 0.06) and the ultraviolet spectrum of the cation does not show the foregoing anomaly.[34]

In addition to having typical *N*-oxide reactions, quinazoline 3-oxide also shows the same reactivity as quinazoline toward nucleophilic reagents, but the reaction goes a step further by eliminating water[94] as shown in reaction 2d. Oxidation with hydrogen peroxide



[2d]

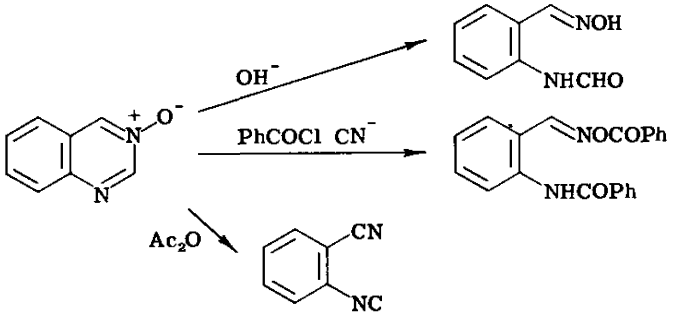
gives 4-hydroxyquinazoline 3-oxide in high yield.[37] Undoubtedly, like quinazoline, a 4-substituent can greatly alter this reactivity.

The *N*-oxide reactions in quinazoline 3-oxide are, however, modified to a certain extent by the aforementioned properties. Thus, whereas it can be reduced to quinazoline with phosphorus trichloride or iron and ferrous sulfate in ethanol, reactions with alkali, acetic anhydride, and benzoyl chloride in the presence of cyanide result in ring fission[94] (Scheme 4).

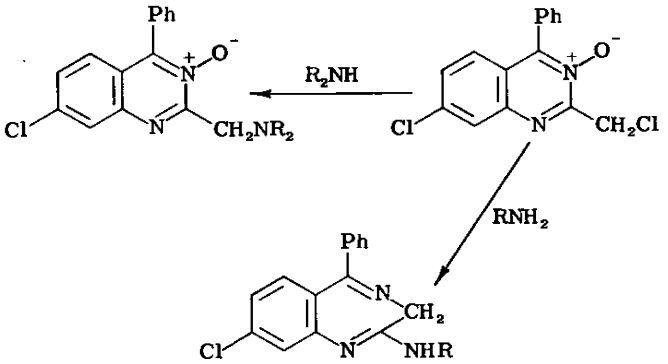
An interesting reaction is the ring enlargement (with rearrangement) caused by primary, but not secondary, amines with appropriately substituted 2-chloromethylquinazoline 3-oxides[95] (Scheme 5).

Quinazoline 1-oxide is not known but 4- and 2,4-substituted quin-

[94] T. Higashino, *Chem. & Pharm. Bull. (Tokyo)* **9**, 635 (1961) (in English).
[95] L. H. Sternbach and E. Reeder, *J. Org. Chem.* **26**, 1111 (1961).

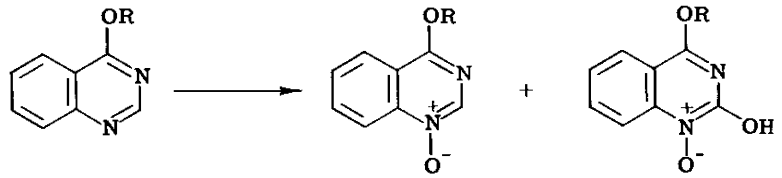


SCHEME 4



SCHEME 5

azoline 1-oxides have been recently prepared by oxidation of the corresponding quinazolines with perphthalic acid,[29,96] and with hydrogen peroxide.[92] In the oxidation with perphthalic acid a small quantity of



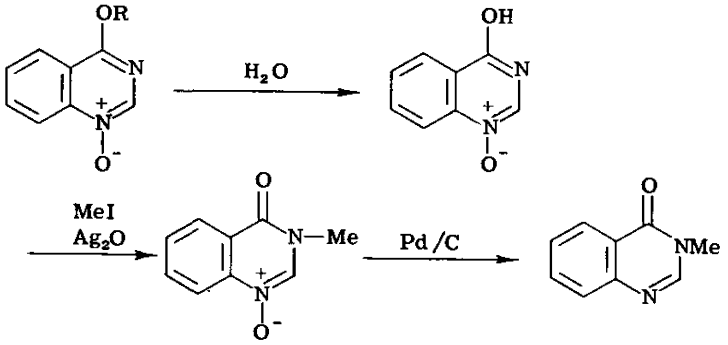
[40]

[where R = Me, Et, Bu, Ph, or $PhCH_2$]

[96] E. Hayashi, H. Yamanaka, and T. Higashino, *Chem. & Pharm. Bull. (Tokyo)* **7**, 149 (1959) (in English); *Chem. Abstr.* **54**, 22665 (1960).

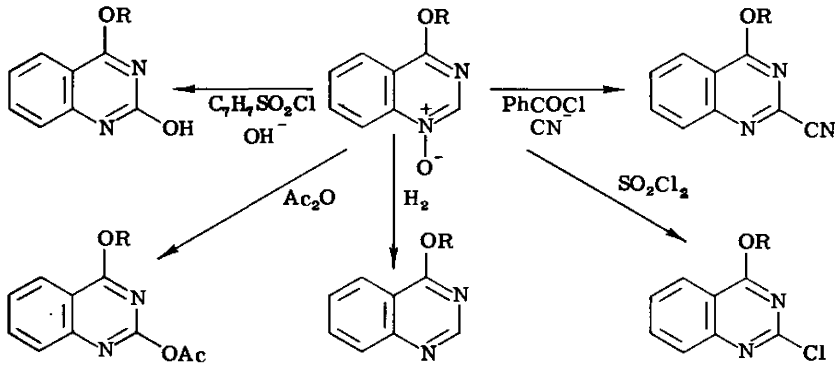
the alkali soluble 2-oxo compound was always formed because the compounds used were unsubstituted in position 2.

The ethers (**40**) are hydrolyzed in high yields, by boiling water (4 hr), to 4-hydroxyquinazoline 1-oxide, and their structures were deduced by methylation followed by reduction to 3-methyl-4(3*H*)-quinazolinone[29] (Scheme 6). These N-1 oxides show the typical reac-



SCHEME 6

tions[94,97] presented in Scheme 7.



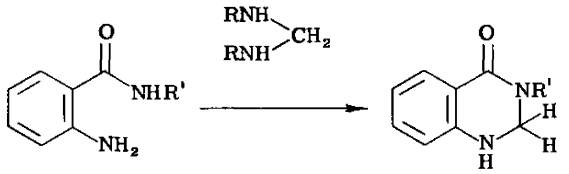
SCHEME 7

V. Hydroquinazolines (Preparation and Properties)

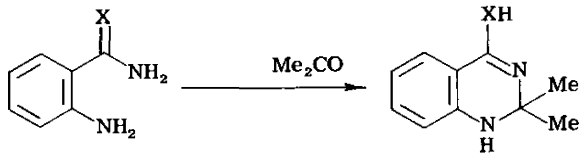
1,2-Dihydroquinazoline is not known but derivatives of 1,2-dihydro-4(3*H*)quinazolinones with a substituent on N-3 have been prepared

[97] T. Higashino, *Yakugaku Zasshi* **79**, 699, 831 (1959) (English Summaries); *Chem. Abstr.* **53**, 21997 (1959).

from substituted anthranilamides using formaldehyde or methylenediamines which acted in a similar way.[98] Similarly 2,2-dimethyl de-



rivatives [e.g. (41)] were obtained by using acetone in place of formaldehyde.[99] In the dihydro compound (41) when X is SH it can be methylated and the resulting thioether group replaced by amines in the usual way. 5,6-Benzo-1,2-dihydro-4(3*H*)quinazolinone was pre-

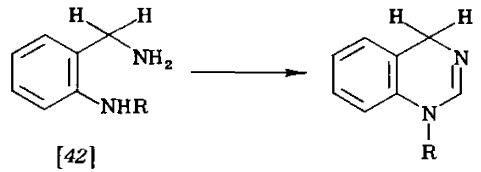


[41]

pared by reduction of 5,6-benzo-4-hydroxyquinazoline with lithium aluminum hydride.[100]

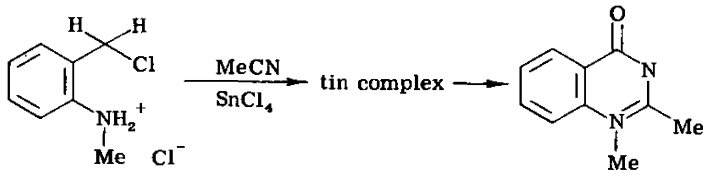
1,4- and 3,4-Dihydroquinazolines are tautomeric but any attempts to prepare the former without a 1-substituent have led to the latter. The greater stability to prototropic change of 1,2-dihydronaphthalene over 1,4-dihydronaphthalene is also found in 3,4-dihydroquinazoline.[44] Earlier claims to the preparation of 1,4-dihydroquinazolines[101] were erroneous and based on incomplete experimental data. The first 1,4-dihydroquinazoline was prepared as recently as 1961.[44] 1-Methyl and 1-benzyl-1,4-dihydroquinazolines were obtained from *o*-methylamino- and *o*-benzylamino-benzylamines (42) by formylation and ring closure. Attempts to remove the benzyl group gave 3,4-dihydroquinazoline. These 1,4-dihydro compounds are susceptible to oxidation, and attempts made to prepare 1,2-dimethyl-1,4-dihydroquinazoline from *o*-

[98] J. R. Feldman and E. C. Wagner, *J. Org. Chem.* **7**, 31 (1942).
[99] H. C. Carrington, *J. Chem. Soc.* p. 2527 (1955).
[100] A. Etienne and M. Legrand, *Compt. rend. acad. sci.* **229**, 1372 (1949).
[101] A. Bischler, *Ber. deut. chem. Ges.* **26**, 1891 (1893).



[42]

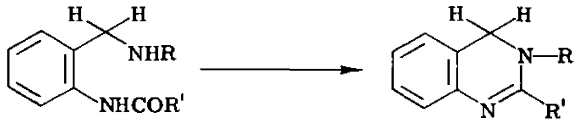
methylaminobenzyl chloride hydrochloride (43) and acetonitrile in the presence of stannic chloride gave 1,2-dimethyl-4(1*H*)quinazolinone.[102] It has, however, been shown by infrared spectra that the tin complex contained the 1,4-dihydroquinazoline. 1-Methyl-1,4-dihydro-



[43]

quinazoline is a hygroscopic liquid. It is a strong base (pK_a 9.43)[12] as expected for a cyclic amidine.

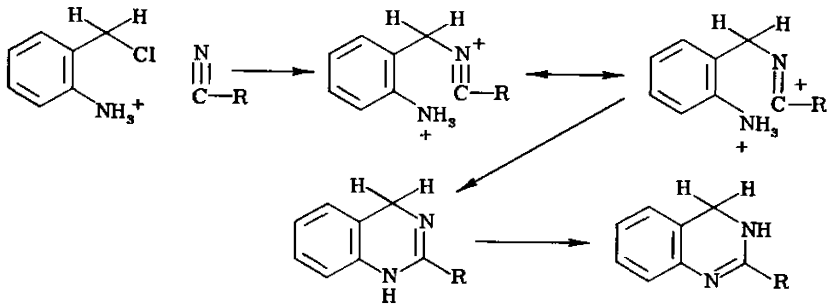
3,4-Dihydroquinazolines are stable and a large number have been prepared. They have been synthesized by reductive cyclization of acyl derivatives of *o*-nitrobenzylamines,[103] and by acylation of *o*-aminobenzylamines followed by ring closure.[28] The ring closure can be effected by heating with anhydrous zinc chloride[101] or by distillation.[44]



Catalytic reduction of quinazolines unsubstituted in position 4 using palladium-charcoal, palladium on calcium carbonate, Raney nickel, or Adam's platinum has been used for preparing 3,4-dihydro-

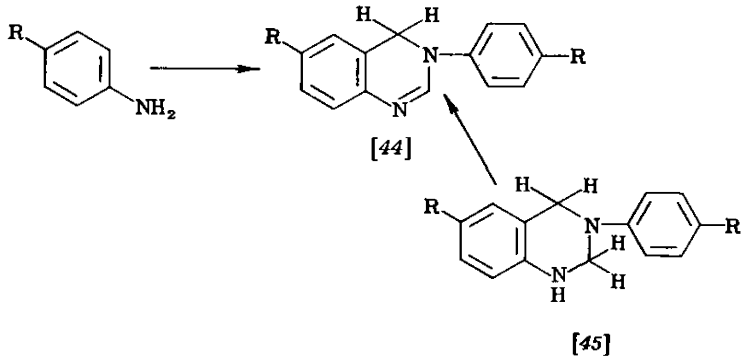
[102] M. Lora-Tamayo, R. Mandroñero, and G. G. Muñoz, *Chem. Ber.* **94**, 208 (1961).
[103] S. Gabriel and R. Jansen, *Ber. deut. chem. Ges.* **23**, 2807 (1890); *ibid.* **24**, 3091 (1891); C. Wolff, *ibid.* **25**, 3030 (1892).

quinazolines.[35] Reduction with Adam's platinum normally stops after absorption of one molecule of hydrogen, possibly owing to poisoning of the catalyst.[44] A large number of 3,4-dihydroquinazolines have been obtained by reaction of *o*-aminobenzyl chloride hydrochloride and its derivatives with alkyl or aryl nitriles in the presence of stannic chloride. One of the mechanisms proposed involves the intermediate formation of 1,4-dihydroquinazolines[102] (Scheme 8).



SCHEME 8

p-Substituted anilines condense with formaldehyde at room temperature to give 3-aryl-3,4-dihydroquinazolines and the reaction has been studied in some detail.[104] The *ortho* positions in the anilines must be available for substitution and, among other products, the tetra-



[44]

[45]

[104] T. R. Miller and E. C. Wagner, *J. Am. Chem. Soc.* **64**, 832 (1941) and previous papers.

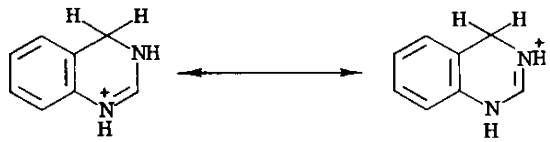
hydroquinazolines (**45**) are formed but these can be oxidized to the dihydro derivatives with manganese dioxide[105] [e.g. (**45**), R = Me]. Oxidation of 1,2,3,4-tetrahydroquinazoline to the 3,4-dihydro derivative has also been achieved with lead tetraacetate and with potassium ferricyanide.[64]

3,4-Dihydroquinazolines are also products of the reaction of quinazoline with nucleophilic reagents (see Section II,B).

3,4-Dihydroquinazolines are normally stable compounds but they deteriorate on long standing. Some examples are known to oxidize to the corresponding 4(3*H*)quinazolinones. 3-Methyl-3,4-dihydroquinazoline is converted to the 4-oxo compound after three recrystallizations from light petroleum.[64] The most remarkable example is 3,4-dihydro-6-fluoro-3(*p*-fluorophenyl)quinazoline [(**44**), R = F] which oxidizes at its melting point (137°–138°C). Other halogenated derivatives of (**44**) are more stable.[106]

3,4-Dihydroquinazolines are oxidized to quinazolines with alkaline potassium ferricyanide (see Section VI,A,1).

The parent substance, 3,4-dihydroquinazoline, is strongly basic (pK_a 9.19)[12,44] on account of the amidinium resonance present in the cation. Spectroscopic evidence favors this resonance and is illustrated



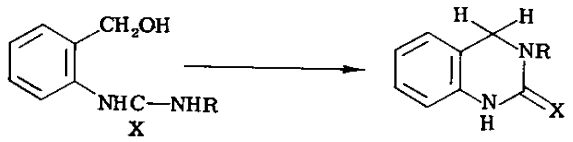
by the close similarity of the ultraviolet spectra of the cations but not the neutral molecules of 1-methyl-1,4-dihydro- and 3-methyl-3,4-dihydro-quinazolines.[12] Substituents in position 4 (SO_3^-, CN, and Me) in 3,4-dihydroquinazoline produce only small and irregular displacement of the major band at 280 mμ, but a hydroxy group in that position (as in hydrated quinazoline and 3-methyl-4-hydroxy-3,4-dihydroquinazoline) causes a large and unexplained hypsochromic shift.[18]

Although some tautomerism between 1,4- and 3,4-dihydroquinazoline is theoretically possible, the dihydro compound always behaves as the 3,4-derivative except, of course, when a substituent is on N-1.

[105] H. M. Fales, *J. Am. Chem. Soc.* **77**, 5118 (1955).
[106] W. V. Farrer, *J. Chem. Soc.* p. 3253 (1954).

Thus dihydroquinazoline is methylated almost exclusively on N-3. Whatever the amount of 1,4-dihydroquinazoline present in equilibrium with 3,4-dihydroquinazoline, the same cation is formed in each case.

3,4-Dihydro-2-hydroxyquinazolines have been prepared by cyclizing *o*-ureidobenzyl alcohols with hydrochloric acid[49] and can be prepared less conveniently from *o*-aminobenzylamines and phosgene[107] (see 3a).

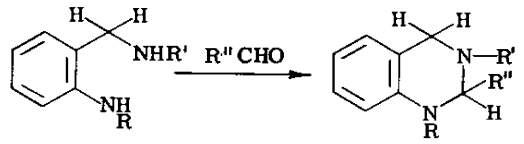


[3a]

[where X = O or S]

The thio analogs are similarly prepared by using carbon disulfide instead of phosgene. These compounds react as cyclic ureas and thioureas.

Further reduction of 3,4-dihydroquinazoline to *1,2,3,4-tetrahydroquinazoline* is more difficult, but it can be accomplished with sodium amalgam[1] or by catalytic reduction with palladium-charcoal.[87] 1,2,3,4-Tetrahydroquinazolines have also been prepared by condensing *o*-aminobenzylamines with various aldehydes[108] and with formaldehyde or methylenediamines[98] (see 3b).

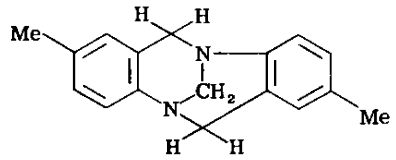


[3b]

Reduction of 3-methyl-4(3*H*)quinazolinone with lithium aluminum hydride is known to give 3-methyl-1,2,3,4-tetrahydroquinazoline.[64]

The most interesting tetrahydroquinazoline is Tröger's base[109] since it has added to our knowledge of the stereochemistry of tri-

[107] M. Busch, *J. prakt. Chem.* [1] **52**, 373 (1895).
[108] M. Busch, *J. prakt. Chem.* [2] **53**, 414 (1896).
[109] J. Tröger, *J. prakt. Chem.* [2] **36**, 227 (1887); see also M. Aroney, L. H. L. Chia, and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 4144 (1961).

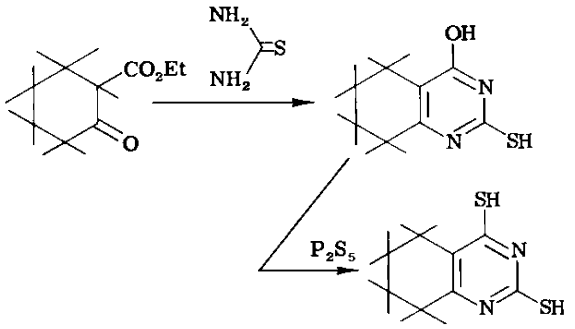


Tröger's base

valent nitrogen. It was resolved by Prelog and Wieland[110] by chromatography on an activated *d*-lactose column, and the highest rotation observed was $[\alpha]_D^{17} = 350°$ ($CHCl_3$).

1,2,3,4-Tetrahydroquinazolines are cyclic methylene diamines and are, therefore, readily hydrolyzed by acid to the corresponding *o*-aminobenzylamines. 1,2,3,4-Tetrahydroquinazoline is a strong base (pK_a 7.65), though it is not as strong as 3,4-dihydroquinazoline because of the absence of amidinium resonance in the cation. The ultraviolet spectrum is only slightly altered on protonation clearly indicating that it takes place on N-3.[12]

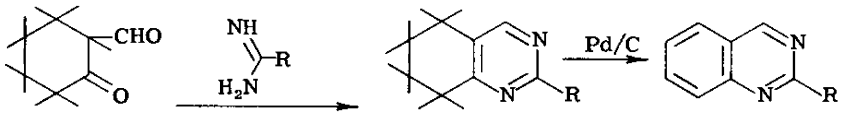
5,6,7,8-Tetrahydroquinazolines are more conveniently classified as 4,5-tetramethylene pyrimidines and their reactions are accordingly typical of pyrimidines. 2,4-Disubstituted derivatives have been prepared by condensation of 1-ethoxycarbonyl cyclohexanones with ureas and thioureas[111,112] (Scheme 9). For monosubstituted derivatives the



SCHEME 9

[110] V. Prelog and P. Wieland, *Helv. Chim. Acta* **23**, 1127 (1944).
[111] F. H. S. Curd, D. N. Richardson, and F. L. Rose, *J. Chem. Soc.* p. 378 (1946).
[112] J. I. De Graw, L. Goodman, and B. R. Baker, *J. Org. Chem.* **26**, 1156 (1961).

condensation of 1-formyl cyclohexanone with amidines yields 2-alkyl- or 2-aryl-5,6,7,8-tetrahydroquinazolines, and these have been dehydrogenated in good yields to 2-alkyl- or aryl-quinazolines[113] (Scheme 10).

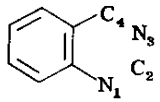


SCHEME 10

The parent substance, a high boiling liquid (bp 225°–230°C), was prepared by replacing the amidine by formamide.[114]

VI. Methods of Preparation

The usual syntheses of quinazolines make use of an *o*-disubstituted benzene structure (**46**) from which the quinazoline skeleton is completed by adding C-2 and N-3 in various ways. Substituents could either be in (a) the pyrimidine ring or (b) the benzene ring or in both rings. The syntheses will be described in this order and the methods used for (a) apply equally well to quinazolines substituted in both rings.



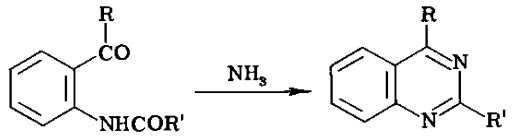
[46]

A. Quinazolines Substituted in the Pyrimidine Ring

1. *Alkyl- and Aryl-quinazolines*

These quinazolines are obtained in high yields by heating *o*-acyl (and formyl) anilides in a sealed tube with saturated alcoholic ammonia for a few hours[42,115] (see 4a). A variant of this method

[113] H. E. Baumgarten, P. L. Greger, and C. E. Villars, *J. Am. Chem. Soc.* **80**, 6609 (1958).
[114] H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.* **90**, 942 (1957).
[115] K. Schofield, T. Swain, and R. S. Theobald, *J. Chem. Soc.* p. 1924 (1952).



[4a]

involves the passage of ammonia through a fused mixture of the *o*-ketoanilides and sodium acetate at 165°–175°C.[74,116]

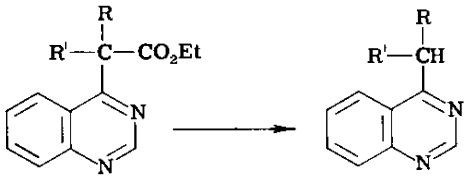
Oxidation of 3,4-dihydroquinazolines with alkaline potassium ferricyanide gives quinazolines in good yields[1,33,35,45] (see 4b). This oxi-

[4b]

[R = H, Me, Ph, CN]

dizing agent is quite specific and other oxidizing agents (e.g., $KMnO_4$ and H_2O_2) are not as satisfactory. When R is *t*-butyl, however, oxidation with ferricyanide yields quinazoline with elimination of the *t*-butyl group.[34]

Decarboxylation of α-(4-quinazolinyl)acetic esters in alkaline solution is useful for the preparation of less readily accessible 4-alkyl quinazolines (see 4c). This method is limited to derivatives where

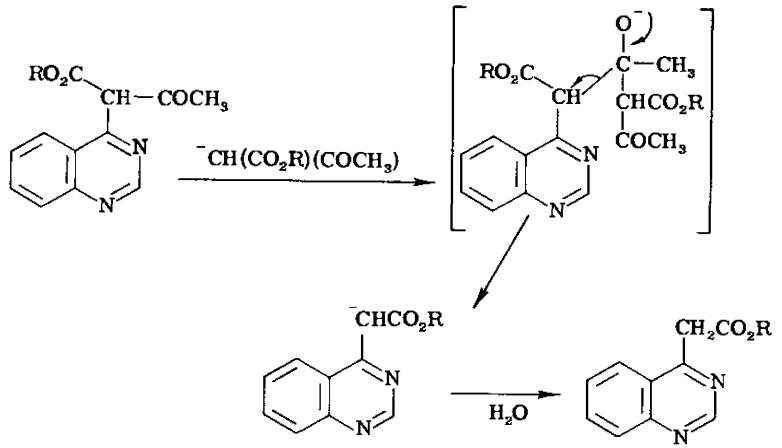


[4c]

R = alkyl, aryl, or CO_2Et and R′ = H.[47] Acid hydrolysis, particularly when R′ = CN or CO_2Et, leads to cleavage of a C—C bond with the formation of 4-hydroxyquinazoline. Sodiodiethylmalonate condenses with 4-chloroquinazoline to give diethyl 4-quinazolinylmalonate (a reaction claimed to be highly unusual for a heterocyclic chloro compound[47]) whereas sodioethylacetoacetate[47] or sodiobenzylacetoacetate[12]

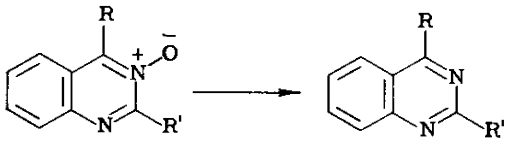
[116] K. Schofield, *J. Chem. Soc.* p. 4034 (1954).

yield, respectively, ethyl and benzyl 4-quinazolinylacetate with loss of the acetyl group. The mechanism postulated for the cleavage of the intermediate 4-quinazolinylacetoacetate is presented in Scheme 11.



SCHEME 11

Reduction of pyrimidine substituted quinazoline 3-oxides, catalytically or with phosphorus trichloride, also leads to quinazolines.[41,92]



When *o*-aminobenzophenone is heated with formamide in the presence of formic acid at 150°C for 20 min, a quantitative yield of 4-phenylquinazoline is obtained.[117] In the absence of formic acid longer heating is necessary. Although this reaction does not proceed with *o*-acylamidobenzophenones, its extension to other *o*-acylanilines with aliphatic amides may prove fruitful.

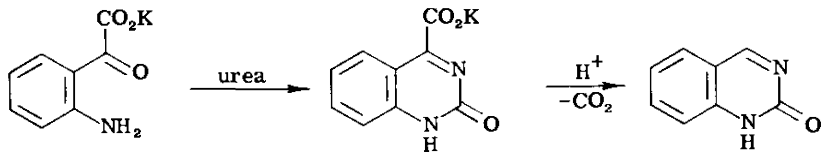
2. *Hydroxyquinazolines*

Hydroxyquinazolines (quinazolinones) are, in solution, a tautomeric

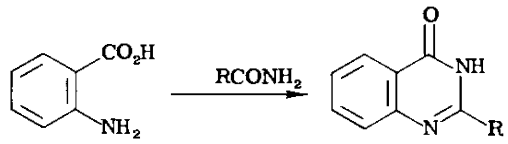
[117] S. Palazzo, *Boll. sedute accad. Gioenia sci. nat. Catania* **71** (227), 75 (1959); *Chem. Abstr.* **55**, 12412 (1961).

mixture of the lactam and the lactim form. For simplicity they are referred to as hydroxy compounds, but only when N-1 or N-3 is unsubstituted, and are normally drawn in the lactam form. The *Chemical Abstracts* nomenclature is adopted for N-1 and N-3 derivatives of hydroxyquinazolines, i.e., 3- and 1-methyl derivatives are written as 3-methyl-4(3*H*)quinazolinone and 1-methyl-4(1*H*)quinazolinone, respectively. These compounds form the largest group of known quinazoline derivatives. This abundance is due to the ease of their preparation from accessible intermediates so that they have often been used as the source of other quinazolines.

2-Hydroquinazolines have been prepared by fusing *o*-acyl (and formyl) anilines with urea,[118] and the parent substance has also been prepared by fusing potassium isatinate with urea or urethane followed by decarboxylation.[119]



4-Hydroxyquinazolines are most conveniently obtained by the Niementowski reaction[120] whereby an anthranilic acid is fused with an aliphatic amide. This reaction has been used extensively and the yields are generally over 50%.[21,121-123]



[47]

[118] S. Gabriel and T. Posner, *Ber. deut. chem. Ges.* **28**, 1029 (1895); S. Gabriel and R. Stelzner, **29**, 1300 (1896).

[119] G. J. Stefanavić, Lj. Lorenc, and M. Lj. Michaelović, *Rec. trav. chim.* **80**, 149 (1961).

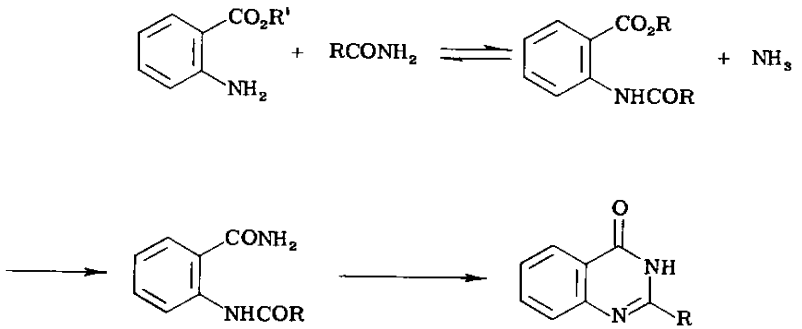
[120] V. Niementowski, *J. prakt. Chem.* [2] **51**, 564 (1895).

[121] A. B. Ben and P. R. Singh, *J. Indian Chem. Soc.* **36**, 787 (1959).

[122] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 141 (1952).

[123] W. L. F. Armarego, *J. Appl. Chem.* **11**, 70 (1961).

It was found inadvisable to use more than four molecules of formamide [(47) when R = H] per molecule of anthranilic acid and the condensation produces best results when the mixture is heated at 120°–130°C for 2 hr followed by further heating at 170°–180°C for 2 hr. Other variants of this reaction involve the use of ammonium *o*-acylaminobenzoates, anthranilic acid in the presence of nitriles and acetic anhydride, *o*-acetamidonitrile with acetic anhydride or hydrogen peroxide, anthranilic esters and aliphatic or aromatic amides or amidines, isatoic anhydride with amides or amidines,[124] and anthranilic esters with aryl iminochlorides in acetone.[125] The mechanism proposed by Bogert and Gotthelf[126] has had experimental support[124] and is represented in Scheme 12.

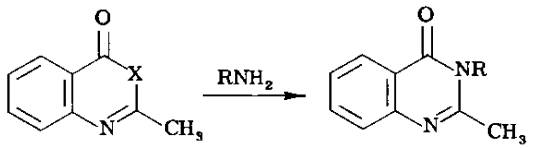


SCHEME 12

In cases where decarboxylation is anticipated, the quinazolinone could be obtained by heating ammonium *o*-formamidobenzoate or *o*-formamidobenzamide for several hours.[127,128] This ring closure could be effected more conveniently by boiling the *o*-formamidobenzamide with 3% aqueous sodium hydroxide for a few minutes.[122,128] *o*-Aminobenzamides have also been converted to quinazolinones by refluxing with ethyl orthoformate alone or preferably in the presence of acetic anhydride.[129,130]

[124] See J. F. Meyer and E. C. Wagner, *J. Org. Chem.* **8**, 239 (1943) for cross references.
[125] P. R. Levy and H. Stephen, *J. Chem. Soc.* p. 985 (1956).
[126] M. T. Bogert and A. H. Gotthelf, *J. Am. Chem. Soc.* **22**, 129 (1900).
[127] M. T. Bogert and H. S. Steiner, *J. Am. Chem. Soc.* **27**, 1327 (1905).
[128] A. Ahmed, N. S. Narang, and J. N. Ray, *J. Indian Chem. Soc.* **15**, 152 (1938).
[129] R. H. Clarke and E. C. Wagner, *J. Org. Chem.* **9**, 55 (1944); M. K. McKee, R. L. McKee, and R. W. Bost, *J. Am. Chem. Soc.* **69**, 184 (1947).

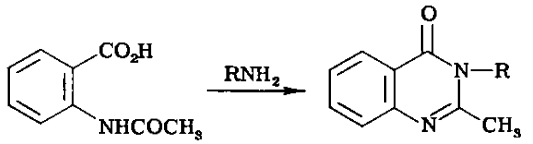
Acetanthranils react exothermically with amines to yield 2,3-disubstituted 4-quinazolinones[58,130–132] (see 5a). 2,3-Disubstituted



[5a]

[R = H,allyl,aryl,NH_2,OH,or CH_2CO_2H and X = O or S]

4(3*H*)quinazolinones, which are derivatives of the lactam form of 4-hydroxyquinazoline, are also readily obtained by boiling a solution of *o*-acylamidobenzoic acid in an inert solvent with the required

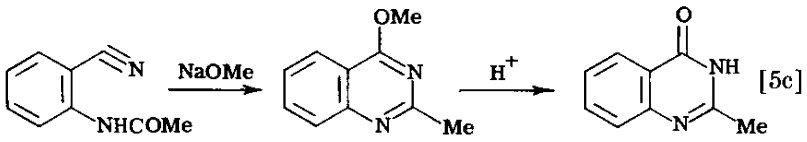


[5b]

amine in the presence of phosphorus trichloride or oxychloride[133] (see 5b). *o*-Acylaminobenzoic esters have also been used in this type of reaction.[134]

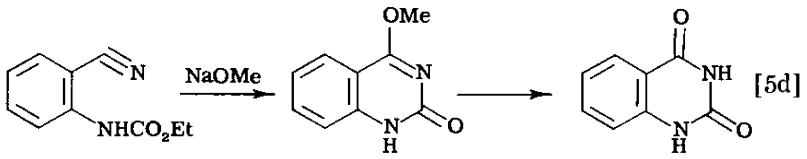
o-Acylaminobenzonitriles are successfully converted to 4-methoxyquinazolines which are easily hydrolyzed to the corresponding 4-hydroxy compounds[75] (see 5c). More than one molecular proportion of methoxide is necessary for the reaction in order to avoid deacylation. This method is superior to the earlier reactions with *o*-acyl-

[130] B. R. Baker, M. V. Querry, A. F. Kadish, and J. H. Williams, *J. Org. Chem.* **17**, 35 (1952).
[131] M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.* **27**, 649 (1905); M. T. Bogert and H. A. Seil, *ibid.* **28**, 884 (1906); P. A. Petyunin and Yu. V. Kozhevnikov, *Zhur. Obshchei Khim.* **30**, 2352 (1960).
[132] L. Legrand and N. Lozach, *Bull. Soc. chim. France* **7**, 1400 (1961).
[133] G. S. Mewada, S. R. Patel, and N. M. Shah, *J. Indian Chem. Soc.* **32**, 199, 483 (1955); R. S. Salimath, S. R. Patel, and N. M. Shah, *ibid.* **33**, 140 (1956); G. Serventi and R. Marchesi, *Boll. sci. fac. chim. ind. Bologna* **15**, 117 (1957) and *Chem. Abstr.* **52**, 9147 (1958); Josef Klosa, *J. prakt. Chem.* [4] **14**, 84 (1961).
[134] F. Dallacker, D. Hollinger, and M. Lipp, *Monatsh. Chem.* **91**, 1134 (1960) and previous papers.

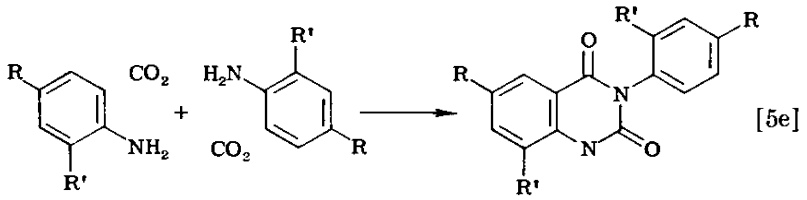


aminobenzonitriles[135] and may find future application in view of the now more ready accessibility of *o*-aminobenzonitriles[136] from isatin oximes.

2,4-Dihydroxyquinazoline (benzoylene urea) has been prepared by fusing urea with anthranilic acid[137] or better from 2-ureidobenzoic acid.[138] It can also be prepared from *o*-ethoxycarbonylaminobenzonitrile and sodium methoxide followed by hydrolysis[139] (see 5d).



Heating arylamines with carbon dioxide at 200°C (8500 atm) gives good yields of 3-aryl derivatives of 2,4-dihydroxyquinazoline[140] (see 5e). The method is unsatisfactory when nitro, halo, and phenolic anilines and α- or β-naphthylamines are used.



3. *Chloroquinazolines*

Chloroquinazolines are obtained from the corresponding hydroxy

[135] M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.* **24**, 1031 (1902).
[136] G. R. Bedford and M. W. Partridge, *J. Chem. Soc.* p. 1633 (1959).
[137] F. E. Sheibley, *J. Org. Chem.* **12**, 743 (1947).
[138] N. A. Lange and F. E. Sheibley, *Org. Syntheses Collective Vol.* **II**, 79 (1943).
[139] K. W. Breukink and P. E. Verkade, *Rec. trav. chim.* **79**, 443 (1960).
[140] T. L. Cairns, D. D. Coffman, and W. W. Gilbert, *J. Am. Chem. Soc.* **79**, 4405 (1957).

compounds and are valuable intermediates for the preparation of a large number of quinazolines substituted in the pyrimidine ring. These chlorinations are best accomplished when a little more than one equivalent of phosphorus pentachloride is used in phosphorus oxychloride. Whereas the latter alone is rarely satisfactory, an excess of phosphorus pentachloride in phosphorus oxychloride has been found sometimes to cause further chlorination.[57,75,100]

2-Chloroquinazoline can be isolated, at best in 40% yield, by boiling 2-hydroxyquinazoline with phosphorus pentachloride in phosphorus oxychloride for 45 min,[118] and attempts to improve this yield have proved fruitless. The yields are much higher when an aryl group[45] is in position 4 which suggests an attack of the 3,4-double bond in 2-hydroxy- and 2-chloro-quinazolines by the chlorinating agent.

A large number of 4-chloroquinazolines have been prepared by the method described for the 2-chloro compound using the respective 4-hydroxyquinazolines.[21,121,123] The reaction time depends on the solubility of the hydroxy compound and on its reactivity. The hydroxyquinazoline and phosphorus pentachloride in phosphorus oxychloride are usually boiled until a clear solution is obtained followed by further boiling for 15–30 min in order to complete the reaction. The working up of the product depends greatly on the lability of the product. When the halogen atom is very reactive, as in 4-chloroquinazoline, condensation of it with 4-hydroxyquinazoline[70] (from starting material or formed by hydrolysis) leads to poorer yields. This difficulty is overcome by removal of the 4-hydroxy compound (e.g., by chromatography over alumina).[12,33,123] Sublimation has been used[11] for purifying chloroquinazolines but this is not advisable because of the risk of self-quaternization.

2,4-Dichloroquinazolines have been prepared from the corresponding 2,4-dihydroxy compounds by heating for a few hours with phosphorus oxychloride in the presence of dimethylaniline or phosphorus pentachloride.[141] These are more stable than the monochloro compounds and can be distilled in vacuum without appreciable decomposition.

Quinazolines substituted in the pyrimidine ring with fluoro, bromo, or iodo atoms are not known.

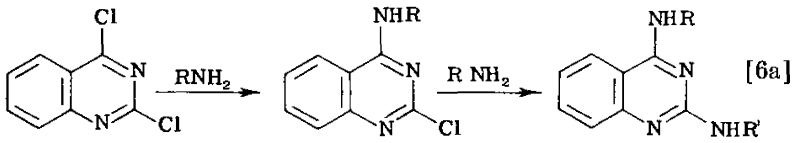
[141] F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.* p. 775 (1947); *ibid.* p. 1759 (1948).

4. *Ethers*

2-, 4-, and 2,4-Alkyl- and aryl-ethers are best prepared from the corresponding chloroquinazolines and metal alkoxide or aryloxide.[142]

5. *Aminoquinazolines*

Aminoquinazolines have been the subject of considerable investigation and a large number of derivatives have been prepared as potential antimalarials. The secondary and tertiary amino compounds can be prepared from the corresponding chloroquinazolines and the required primary or secondary amines.[60,121,143,144] The reaction depends on the reactivity of the halogen atom, e.g., the 4-chloro atom reacts more readily than the 2-chloro atom in quinazolines[68,145] and also on the basic strength of the amine used[146] (see 6a). The reaction is

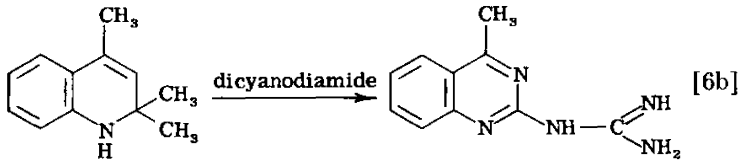


[6a]

normally carried out by heating the chloroquinazoline with the amine in ethanol in a sealed tube,[147] or in the case of nonvolatile amines, by refluxing in an inert solvent (e.g., nitromethane) or without a solvent.[148]

2-Aminoquinazoline is best obtained by boiling *o*-aminobenzaldehyde with guanidine carbonate in Decalin.[80] *o*-Acylanilines, also react with cyanoguanidines to give 2-guanidinoquinazolines.[149] An extension of this method makes use of acetone anil as the source of *o*-aminoacetophenone[150] (see 6b).

[142] N. A. Lange, W. E. Roush, and H. J. Asbek, *J. Am. Chem. Soc.* **52**, 3696 (1930).
[143] A. Kötz, *J. prakt. Chem.* [2] **47**, 303 (1893).
[144] S. Biniecki and E. Muszynski, *Acta Polon. Pharm.* **17**, 99 (1960); *Chem. Abstr.* **54**, 21119 (1960).
[145] E. Vopica and N. A. Lange, *J. Am. Chem. Soc.* **57**, 1068 (1935).
[146] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* p. 1014 (1949).
[147] M. J. S. Dewar, *J. Chem. Soc.* p. 619 (1944).
[148] N. B. Chapman and H. Taylor, *Chem. Soc.* p. 1908 (1961).
[149] L. F. Theiling and P. L. McKee, *J. Am. Chem. Soc.* **74**, 1834 (1952).
[150] J. P. Brown, *Chem. & Ind. London* No. 9, p. 233 (1960).



[6b]

Direct replacement of methoxy, mercapto, and methylmercapto groups by amino or substituted amino groups has been used for the preparation of 4-alkylaminoquinazolines.[60,151] Some 2-alkylaminoquinazolines have been prepared most conveniently by displacement of the methylmercapto group[84] (see 6c).

[6c]

[where X = OMe, SH, SMe]

2-Aminoquinazoline has also been prepared by fusing a mixture of potassium isatinate and guanidine followed by decarboxylation of the resulting 2-aminoquinazoline 4-carboxylic acid.[119]

o-Aminobenzonitriles undergo intermolecular condensations with aromatic nitriles in basic media to give 2-aryl-4-aminoquinazolines in good yields. This reaction constitutes a general method for the synthesis of 4-aminopyrimidine heterocycles[81] (see 6d).

[6d]

6. *Mercaptoquinazolines*

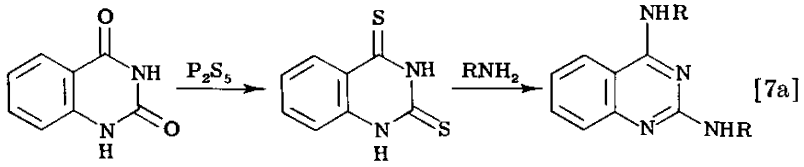
Mercaptoquinazolines can be prepared using methods applicable to hydroxyquinazolines but the rare availability of the intermediates (e.g., *o*-aminodithiobenzoic acid) limits these methods considerably.

2-Mercaptoquinazoline is best obtained from 2-chloroquinazoline

[151] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.* **11**, 349 (1946).

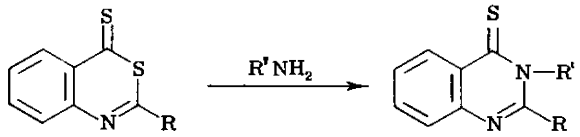
by reaction with an alkali hydrogen sulfide,[1] a method that was previously used to prepare 4-mercapto- and 2,4-dimercapto-quinazolines.[143]

Fusion of 4-hydroxyquinazoline with phosphorus pentasulfide yields 4-mercaptoquinazoline[151] and, similarly, substituted 2,4-dimercaptoquinazolines have been obtained from the corresponding dihydroxy compounds.[85] The greater reactivity of the 4-mercapto as compared with the 2-mercapto group has permitted the preparation of 4-amino-2-mercaptoquinazolines (see 7a).



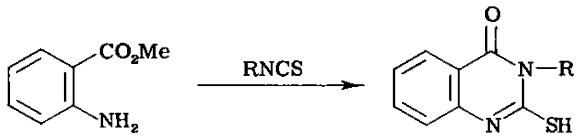
[7a]

2,3-Disubstituted derivatives of 4-mercaptoquinazolines were obtained in good yields by reaction of 5,6-benzo-1,3-thiazine-4-thione with amines[132] (see 7b).



[7b]

3-Substituted 2-mercapto-4(3*H*)quinazolinones were prepared by condensing methyl anthranilate with isothiocyanates[152] (see 7c).



[7c]

B. Quinazolines Substituted in the Benzene Ring

A relatively small number of quinazolines unsubstituted in the pyrimidine ring are known. Four distinctly different methods are

[132] J. E. MacCarty, E. L. Haines, and C. A. VanderWerf, *J. Am. Chem. Soc.* **82**, 964 (1960).

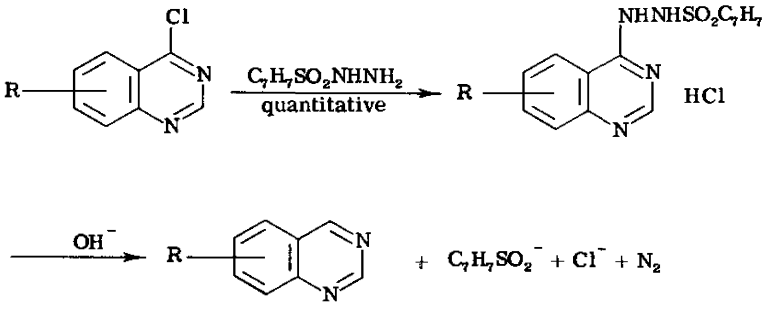
available for the preparation of quinazoline and these have been used for the synthesis of benz-substituted quinazolines.

Dehalogenation of chloroquinazoline has been carried out in a number of ways[1,147] and only the more satisfactory will be described here. 4-Chloroquinazoline has been reduced catalytically with the absorption of two molecular proportions of hydrogen with the formation of 3,4-dihydroquinazoline. The halogen atom in 4-chloroquinazoline is labile enough to be removed before appreciable reduction to the dihydro compound occurs; hence, if the reduction is stopped after absorption of one molecular proportion of hydrogen, a good yield of quinazoline can be obtained. 4-Chloroquinazoline is hydrolyzed readily in acid solution and reductions are carried out using palladium on calcium carbonate[35] or palladium on magnesium oxide.[33] A more satisfactory way of keeping the solution basic is to hydrogenate with 10% palladium on charcoal in the presence of 1.5 equivalents of sodium acetate.[123] The method, which depends on the reactivity of the halogen atom, was found unsatisfactory when the rate of dehalogenation was of the same order as the rate of reduction to 3,4-dihydro- and 1,2,3,4-tetrahydro-quinazolines.[21] This is a serious limitation because the reactivity of the halogen atom in benz-substituted 4-chloroquinazolines is influenced by the nature and position of the substituent. Furthermore this method cannot be applied to the preparation of substituted quinazolines with reducible groups (e.g., NO_2, CN).

The oxidation of 3,4-*dihydroquinazolines* has been used to prepare 6- and 8-aminoquinazolines among others.[11,35]

Of greater versatility is an extension of Albert and Royer's acridine synthesis.[153] The first successful use of this in the quinazoline series was for the removal of the chlorine atom in 2-chloro-4-phenylquinazoline,[45] although it had been used previously to prepare 8-nitro-6-methoxyquinazoline in very poor yield.[147] The 4-chloroquinazoline is converted to its 4-(*N'*-toluene-*p*-sulfonylhydrazino)quinazoline hydrochloride derivative which is decomposed with alkali in aqueous ethylene glycol at 100°C (Scheme 13). The yields are high (60–70%) when R is Me, Cl, OMe but low when R is NO_2, and in the latter case it is preferable to use dilute sodium carbonate as the base.[21] This reaction is unsatisfactory if the unsubstituted pyrimidine ring is unstable towards alkali, as in 1,3,8-triazanaphthalene where the pyrimi-

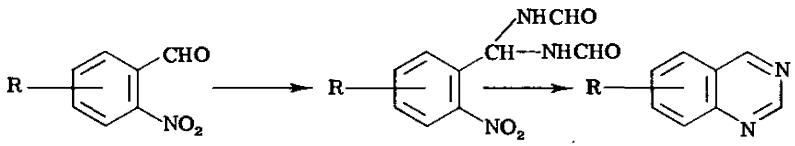
[153] A. Albert and R. Royer, *J. Chem. Soc.* p. 1148 (1949).



SCHEME 13

dine is degraded by dilute alkali,[26] and, apparently, 2.2 equivalents of alkali are sufficient to bring about the decomposition of the hydrazino derivative. The reaction time varies from 1 to 2 hr, and the reaction is completed when nitrogen evolution stops. This is the only method available for preparing quinazolines with reducible groups.

An old and satisfactory method is the *Riedel* synthesis[154] in which *o*-nitrobenzaldehyde is converted to its bisformamido derivative followed by reductive cyclization with zinc and acetic acid, or with iron and hydrochloric acid.[155] This synthesis has been used to make



SCHEME 14

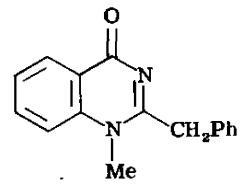
various quinazolines,[21,82,156] but its application is limited by the poor availability of substituted *o*-nitrobenzaldehydes (Scheme 14).

Reduction of *quinazoline oxides* to quinazolines, catalytically (Raney nickel, palladium on charcoal) or with iron and ferrous sulfate in 85% alcohol can be extended to the preparation of benz-substituted quinazolines.[37,41]

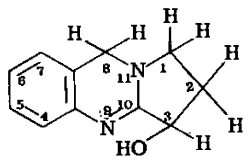
[154] A. Riedel, German Patent 174,941 (1905), see M. T. Bogert and E. M. McColm, *J. Am. Chem. Soc.* **49**, 2650 (1927).
[155] K. Adachi, *Yakugaku Zasshi* **75**, 1423 (1955); *Chem. Abstr.* **50**, 10105 (1956).
[156] A. Albert and A. Hampton, *J. Chem. Soc.* p. 4985 (1952).

VII. Quinazoline Alkaloids

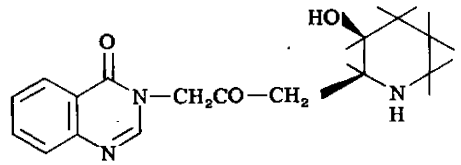
Alkaloids containing a quinazoline nucleus form a small but important group of natural products and have been isolated from a number of different families in the plant kingdom. The quinazoline alkaloids are of the four types: **(48)**, **(49)**, **(50)**, and **(51)**. The structures of arborine,[156a] peganine, febrifugine, rutaecarpine, and evodiamine have been elucidated by degradation and synthesis and are described in recent reviews on quinazoline alkaloids.[157]



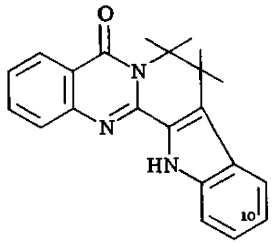
Arborine
[48]



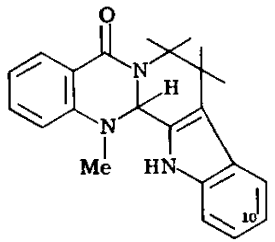
Peganine (vasicine)
[49]



Febrifugine
[50]



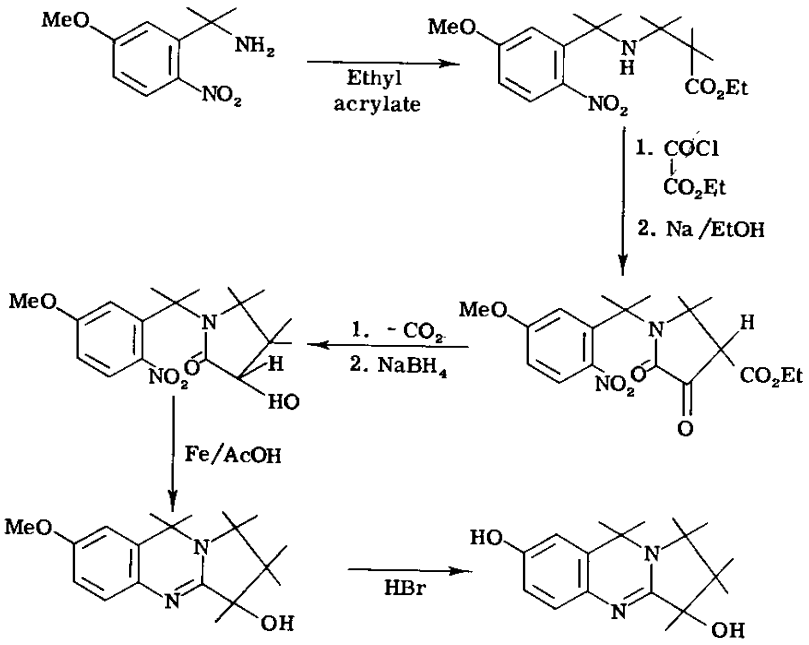
Rutaecarpine
[51a]



Evodiamine
[51b]

[156a] Compare D. Chakravarti *et al.* (6 authors), *Tetrahedron* **16**, 224 (1961).
[157] J. R. Price, *Fortschr. Chem. org. Naturstoffe* **13**, 330 (1956); H. T. Openshaw, *Alkaloids* **3**, 101 (1953) and *ibid.* **7**, 247 (1960).

Peganine, also referred to as 3-hydroxypegane was first isolated from the leaves of the Indian plant *Adhatoda vasica* Nees and has been used for the treatment of asthma. Recently Späth and Keoztler-Gandini[158] have isolated *l*-peganine, contaminated with an alkaloid, which they purified. The analytical figures indicated a hydroxy-peganine. It differed from peganine in being dextrorotatory. This substance was identical with 6-hydroxypeganine[159] and synthesized by a route recently developed for *dl*-peganine[160] (Scheme 15).



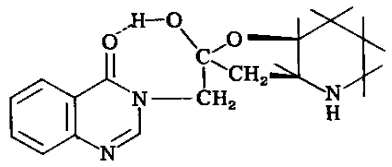
SCHEME 15

Peganine has two nitrogen atoms and its monoacidity is due to the formation of a cyclic amidinium cation. The Schöpf-Oechler[31,161] scheme for the synthesis of peganine from *o*-aminobenzaldehyde and

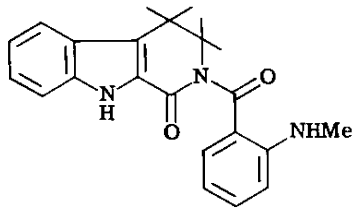
[158] E. Späth and F. Keoztler-Gandini, *Monatsh. Chem.* **91**, 1150 (1960).
[159] F. Kuffner, G. Lenneis, and H. Bauer, *Monatsh. Chem.* **91**, 1152 (1960).
[160] P. L. Southwick and J. Casanova, *J. Am. Chem. Soc.* **80**, 1168 (1958).
[161] L. Macholan, *Collection Czechoslov. Chem. Commun.* **24**, 550 (1959); L. Skursky, *Z. Naturforsch.* **14B**, 474 (1959).

γ-amino-α-hydroxybutyraldehyde under "physiological conditions" has been repeated[162] and *dl*-peganine was isolated in 39% over-all yield.

The structure of febrifugine (the famous Chan' San alkaloid known since 200 B.C.) has been completely elucidated, but that of the isomer isofebrifugine which occurs with it is still in some doubt. All evidence points to the semiketal structure (**52**) and, although it is readily converted to febrifugine, it does not react with ketonic reagents.



[*52*]

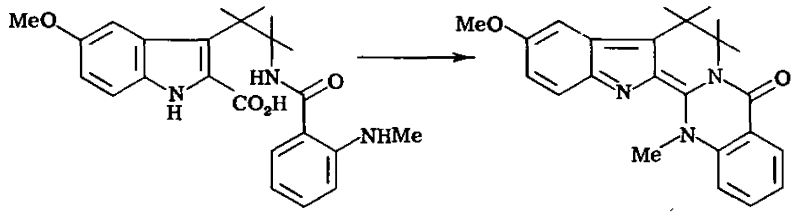


[*53*]

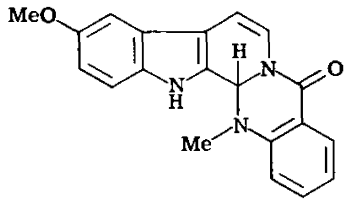
Evodiamine, the alkaloid from the Chinese drug plant *Evodia rutaecarpa* Benth. and Hook., has also been called rhetsine[163] and its oxidation product rhetsinine, which is also found in nature, was shown to be the diamide (**53**).[164] Recently a hypotensive red alkaloid isolated from the Brazilian plant *Hortia arborea* Engl. was given the name hortiamine.[165] Degradation and synthetic studies have shown it to possess the structure (**55**). It was found together with another

[162] N. J. Leonard and M. J. Martell, Jr., *Tetrahedron Letters* No. 25, 44 (1960).
[163] A. Chatterjee, S. Bose, and C. Ghosh, *Tetrahedron* **7**, 257 (1959); see also K. W. Gopinath, T. R. Govindachari, and U. Ramatas Rao, *ibid.* **8**, 293 (1959).
[164] I. J. Pachter and G. Guld, *J. Org. Chem.* **25**, 1680 (1960).
[165] I. J. Pachter, R. F. Raffauf, G. E. Ullyot, and O. Ribiero, *J. Am. Chem. Soc.* **82**, 5187 (1960).

very closely related alkaloid, hortiacine, which is 10-methoxy rutaecarpine. Hortiamine has also been isolated from *Hortia braziliana* Vel. and synthesized in quantitative yield by reaction of the accessible amide (**54**) with polyphosphoric acid.[166] The chemistry of hortiamine



[*54*] Hortiamine [*55*]



Isohortiamine

[*56*]

has been studied in some detail and there is evidence that an isomer, isohortiamine (**56**), also occurs naturally.

Like peganine a laboratory synthesis of rutaecarpine (**51a**) under "physiological conditions" has been realized by condensation of *o*-aminobenzaldehyde with a β-carboline[167] (Scheme 16).

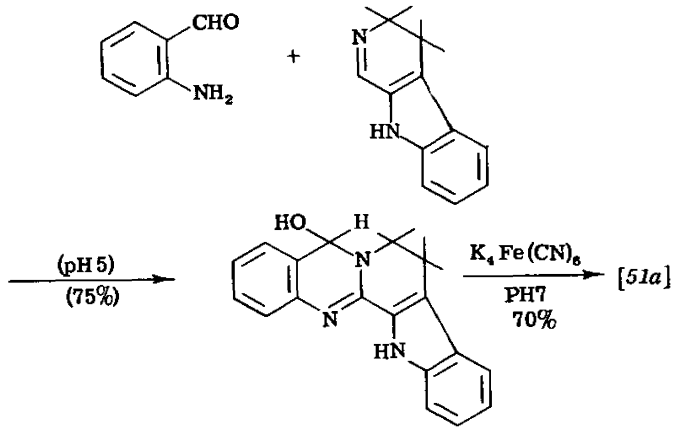
VIII. Biologically Active Quinazolines

Many quinazolines possessing a wide variety of biological activities are known. The antimalarial activity of febrifugine spurred the preparation and testing of a number of quinazolines,[168] and several

[166] I. J. Pachter, R. J. Mohrbacher, and D. E. Zacharias, *J. Am. Chem. Soc.* **83**, 635 (1961).

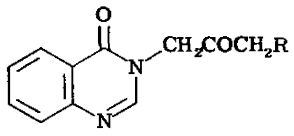
[167] C. Schöpf and H. Steuer, *Ann. Chem. Liebigs* **558**, 124 (1947).

[168] F. W. Wiselogle, "Survey of Antimalarial Drugs 1941–45." Edward Brothers, Ann Arbor, Michigan, 1946.



Scheme 16

patent claims have been made on quinazolines as intermediates for potential antimalarials.[169] The compounds (**57a**) and (**57b**) were shown to have significant antimalarial activity.[170]



[*57*]

[*57a*] R = ω-*N*-morpholylpropyl
[*57b*] R = ω-*N*-piperidyl-*n*-butyl

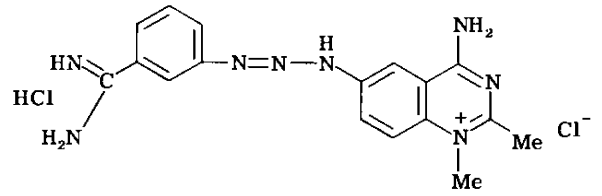
Several 2,3-disubstituted-4(3*H*)quinazolinones were active against *Plasmodium gallinaceum*[171] and showed antiinflammatory action on experimental edemas in animals.[58] 6-(*m*-Amidinophenyldiazoamino)-

[169] B. R. Baker and M. V. Querry (American Cyanamid Co.), U. S. Patent 2,796,417, see *Chem. Abstr.* **52**, 459 (1958); B. R. Baker (American Cyanamid Co.), U. S. Patent 2,811,542, see *Chem. Abstr.* **52**, 5488 (1958).

[170] O. Y. Magidson and Y. K. Lu, *Zhur. Obshcher. Khim.* **29**, 2843 (1959); *Chem. Abstr.* **54**, 12144 (1960).

[171] M. K. Jain and K. S. Narang, *Research Bull. Punjab Univ.* No. 29, 51 (1953); *Chem. Abstr.* **49**, 1603 (1955), M. L. Baumi and M. S. Dhatt, *Current Sci. (India)* **26**, 85 (1957).

4-amino-1,2-dimethylquinazolinium chloride hydrochloride (58) was found very effective against the protozoan parasite *Babesia canis*.[172] It has been patented[173] and is referred to as M. and B.4986.



[58]

Amino- and hydrazino-quinazolines exhibited antibacterial activity[174] and a patent claim on the *in vitro* action of 2,4-diaminoquinazolines was made.[175] The preparation of thiopegan derivatives as potential antimalarials and antibacterials deserves mention.[176]

Complete inhibition of influenza virus *in vitro* but not *in vivo* was shown by 6,8-dichloro-2,4-dihydroxyquinazoline and other cyclic ureas.[177] Activity against trachoma virus was also displayed by several 2-trichloromethylquinazolines.[178]

7-Chloro-6-sulfonamido-4(3*H*)quinazolinones are more effective than the mercury diuretics and can be administered orally.[179] The 1,2-dihydro derivatives are even more effective[180] and one (59) has been marketed under the name "Quinethazone."

2-Alkyl-3-aryl-4(3*H*)quinazolinones affect the nervous system in a

[172] S. S. Berg and J. M. S. Lucas, *Nature* **189**, 64 (1961); S. S. Berg, *J. Chem. Soc.* p. 4041 (1961).

[173] S. S. Berg (May & Baker Ltd.), British Patent 858,814, see *Chem. Abstr.* **55**, 12434 (1961).

[174] K. Asano and S. Asai, *Yakugaku Zasshi* **78**, 450 (1958) (English Summary) and *Chem. Abstr.* **52**, 18428 (1958); L. Niepp, W. Kunz, and R. Meier, *Experientia* **13**, 74 (1957).

[175] G. H. Hitchings, E. A. Falco, K. W. Ledig [Burroughs Wellcome & Co. (U.S.A.), Inc.], U. S. Patent 2,945,859, see *Chem. Abstr.* **54**, 24820 (1960).

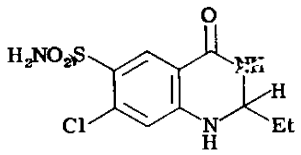
[176] H. S. Sachdev and N. R. Ralhan, *J. Sci. Ind. Research (India)* **19c**, 109 (1960) and earlier papers.

[177] T. W. Chang and I. B. Hudson, *Antibiotics & Chemotherapy* **7**, 443 (1957).

[178] W. Hepworth (Imperial Chemical Industries Ltd.), British Patent 857,362, see *Chem. Abstr.* **55**, 14487 (1961).

[179] J. R. Vaughan, Jr., E. Cohen, and B. Klarberg, *J. Am. Chem. Soc.* **89**, 5508 (1959).

[180] F. C. Novello (Merck & Co., Inc.), U. S. Patent 2,952,680, see *Chem. Abstr.* **55**, 4546 (1961); E. Cohen and J. R. Vaughn, Jr. (American Cyanamid Co.), U. S. Patent 2,976,289, see *Chem. Abstr.* **55**, 17663 (1961).



[59]

number of ways. Indian workers[181] have discussed the potent hypnotic effect in rats of these quinazolinones some of which were clinically satisfactory. Tests have shown that they possess central depressant activity in higher animals comparable to those of the most potent barbiturates.[182] In addition they have a hypothermic (as distinct from antipyretic) effect and the possible use of 2-methyl-3-phenyl-4(3*H*)quinazolinone for producing therapeutic hypothermia was suggested.[183] Similar compounds possessed vasodepressor activity with low toxicity and the 3-benzyl derivatives showed spasmolytic effect without analgesic, antipyretic, antihistamine, anthelminthic, or blood pressure effects.[184] 2-Methyl-3-*o*-tolyl-4(3*H*)quinazolinone was superior to sodium phenobarbitone as an anticonvulsant against metrazol-induced seizures,[185] and among forty compounds tested for oral anticonvulsant activity against leptazol-induced convulsions in mice 2-methyl-*p*-bromophenyl-4(3*H*)quinazolinone hydrochloride (known as B.D.H.1880) was the most active, and is eight times more active than troxidone against electroshock-induced convulsions.[186]

The carcinogenic properties of tricycloquinazoline (60) were studied in detail because of its possible formation from anthranilic acid derivatives in nature.[187] It possessed stronger carcinogenic activity toward mice (72%) than rats (27%). Its action resembled that of embedded plastic materials, because it was recovered unmetabolized.[188]

[181] M. L. Gujral, P. N. Saxena, and R. S. Tiwari, *Indian J. Med. Research* **43**, 637 (1955).

[182] W. M. McLamore, S. Y. P'an, and G. D. Lauback, Abstracts of papers of the 133rd meeting Am. Chem. Soc. April 1958, California, p. 12M. Cf. reference 152.

[183] P. N. Saxena and B. K. Khanna, *Indian J. Med. Research* **46**, 63 (1958).

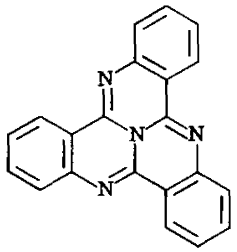
[184] F. Sandberg, *Svensk Farm. Tidskr.* **61**, 453 (1957); *Chem. Abstr.* **51**, 16940 (1957).

[185] M. L. Gujral, K. N. Sareen, and R. P. Kohli, *Indian J. Med. Research* **45**, 207 (1957).

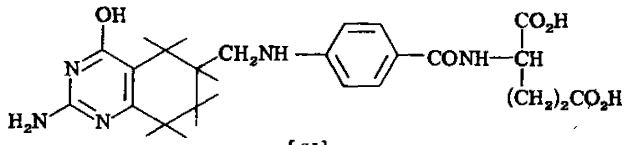
[186] C. Bianchi and A. David, *J. Pharm. and Pharmacol.* **12**, 501 (1960).

[187] F. C. Cooper and M. W. Partridge, *J. Chem. Soc.* p. 3429 (1954).

[188] R. W. Baldwin, G. J. Cunningham, and M. W. Partridge, *Brit. J. Cancer* **13**, 94 (1959).



[60]



[61]

Several tetrahydroquinazoline analogs of folic acid were synthesized by Baker and co-workers[189] as potential anticancer agents, and the substance (**61**), at 50 mμg/ml, gave a 50% inhibition of growth of *Streptococcus faecalis* on a Flynn folic acid medium containing 3 mμg of folic acid.

4-Hydroxy- and 8-nitro-4-chloroquinazolines have been incorporated into the nucleotide of vitamin B_{12}. These quinazoline-containing vitamin analogs stimulated the growth of cobalamine requiring cultures.[190]

Of agricultural importance is the plant-growth regulating activity of 6,8-dichloro-2-methyl-3-carboxymethyl-4(3*H*)quinazolinone which was as potent as 2,4-dichlorophenoxyacetic acid in the Lepidium test.[191] 4-Hydroxy-5,6,7,8-tetrahydroquinazoline has been patented[192] with reference to fungicidal activity.

[189] B. R. Baker, R. Koehler, L. Goodman, and J. De. Graw, *J. Am. Chem. Soc.* **80**, 5779 (1958); *J. Org. Chem.* **26**, 1156 (1961).

[190] D. Perlman and J. M. Barrett, *Can. J. Microbiol.* **4**, 9 (1958).

[191] Lehr-Splawinski, *Zeszyty Nauk. Uniw. Jagiel. Ser. Nauk. Mat., Przyrod. Mat., Fiz., Chem.* No. 6, 53 (1959); *Chem. Abstr.* **55**, 3602 (1961).

[192] A. Margot and H. Gysin (J. R. Geigy A.-G.), U. S. Patent 2,839,446, see *Chem. Abstr.* **52**, 17297 (1958).

IX. Industrial Uses

In addition to the use of some of the foregoing quinazolines in drug manufacture, certain quinazoline derivatives, particularly when condensed with aminoanthraquinones, are claimed as useful dyestuffs.[193] *N*-1,*N*-3-Dichlorobenzoylene ureas are claimed as useful odorless bleaching agents[194] and claims have been made that the addition of chloro- or nitrosubstituted 4-hydroxyquinazolines suppress color stains in color developing solutions or coatings in photography.[195]

ACKNOWLEDGMENT

The author is indebted to Professor Adrien Albert for many helpful discussions during the preparation of this article.

[193] F. Ebel, W. Rupp, and O. Trauth (Badische Anilin- & Soda Fabrik Akt.-Ges.), German Patent 931,845, see *Chem. Abstr.* **52**, 1639 (1958); J. Brassel, A. Fasciati, and A. Buehler (CIBA Ltd.), U. S. Patent 2,773,871, see *Chem. Abstr.* **51**, 5439 (1957).

[194] Thomas Hedley & Co., Ltd., British Patent 847,566, see *Chem. Abstr.* **55**, 8438 (1961).

[195] Agfa-Wolfen, German Patent Appl. V-100895 (1956), see *Repts. Progr. Appl. Chem.* **43**, 88 (1958).

Prototropic Tautomerism of Heteroaromatic Compounds: I. General Discussion and Methods of Study*

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*The last two chapters in this volume are of a series of four, the remaining two to appear in the next volume. Cross references to these articles include, for easy identification, the roman numeral given in the title of chapters.

I. General Discussion

This chapter and the three following chapters are concerned with the tautomerism of five- and six-membered heterocyclic compounds[1] in which at least one of the possible tautomeric structures is aromatic, i.e., a planar ring in which all the annular atoms possess p-orbitals perpendicular to the plane of the ring. Further, these chapters have been limited to prototropy—the movement of hydrogen atoms—and for the most part only those labile hydrogen atoms which are attached either directly to annular atoms or to atoms adjacent to the ring are considered. Finally, only compounds containing nitrogen, oxygen, or sulfur as hetero atoms are considered in detail; compounds with other hetero atoms have received little attention thus far.[2]

General accounts of prototropic tautomerism have been presented by Ingold[3] and Baker[4,5]; these include an outline of the historical development of the subject in which heteroaromatic compounds are discussed incidentally, and, therefore, such a historical account will not be given here. Of historical interest are Eistert's book on tautomerism and mesomerism which was published in 1938,[6] a review on —NH·CO— tautomerism by Arndt and Eistert published in 1938,[7] and Heller's account of heterocyclic tautomerism[8] which appeared in 1925. Although more recent works on heterocyclic chemistry (e.g., references 9–11) have dealt incidentally with tautomerism, no unified

[1] The manifold possibilities for tautomerism in seven-membered heterocyclic systems are virtually unexplored; cf., however, A. H. Rees, *J. Chem. Soc.* p. 3111 (1959).

[2] Within these limitations we have attempted to include references to all relevant work. However, since it is difficult to locate papers dealing only incidentally with tautomerism, there are undoubtedly pertinent references which have been missed. We would be most grateful if these omissions were brought to our attention.

[3] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," pp. 530–575. Cornell Univ. Press, Ithaca, New York, 1953.

[4] J. W. Baker, *in* "Thorpe's Dictionary of Applied Chemistry" (I. M. Heilbron, ed.), Vol. XI, pp. 425–444. Longmans, Green, New York, 1954.

[5] J. W. Baker, "Tautomerism." G. Routledge, London, 1934.

[6] B. Eistert, "Tautomerie und Mesomerie." Enke, Stuttgart, Germany, 1938.

[7] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **71**, 2040 (1938).

[8] G. Heller, A. Buchwaldt, R. Fuchs, W. Kleinicke, and J. Kloss, *J. prakt. Chem.* **111**, 1 (1925).

[9] A. Albert, "Heterocyclic Chemistry." Athlone Press, London, 1959.

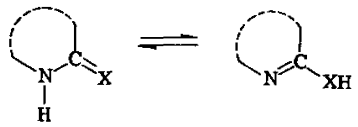
[9a] R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds." Interscience, New York, 1960.

or detailed treatment has been available. Albert's brief, but useful, survey of the tautomerism of six-membered nitrogen heterocycles[12] appeared in 1955.

A. The Principal Types of Tautomerism

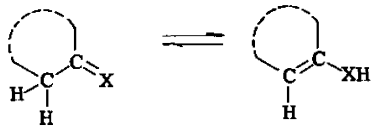
The principal types of tautomerism can be classified according to the nature and the position of the atoms between which the protons move:

(*i*) Annular nitrogen and an atom adjacent to the ring (cf. **1** ⇌ **2**),



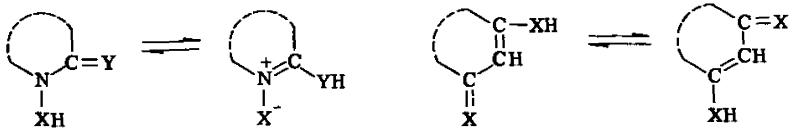
[*1*] [*2*]

(*ii*) Annular carbon and an atom adjacent to the ring (cf. **3** ⇌ **4**),



[*3*] [*4*]

(*iii*) Two atoms adjacent to the ring (cf. **5** ⇌ **6** or **7** ⇌ **8**),



[*5*] [*6*] [*7*] [*8*]

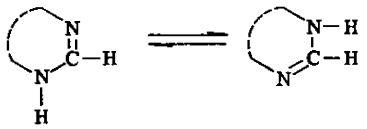
[9b] G. M. Badger, "The Chemistry of Heterocyclic Compounds." Academic Press, New York, 1961.

[10] R. C. Elderfield (ed.), "Heterocyclic Compounds," Vols. I–VII. Wiley, New York, 1950–1961.

[11] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry." Methuen, London, 1960.

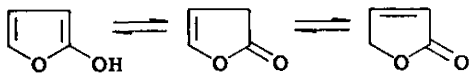
[12] A. Albert, *Chem. Soc. (London), Spec. Publ. No.* **3**, pp. 124–138 (1955).

(*iv*) Two annular nitrogen atoms (cf. **9**⇌**10**),



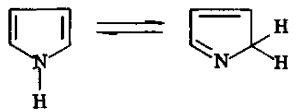
[*9*] [*10*]

(*v*) Two annular carbon atoms (cf. **12**⇌**13**),



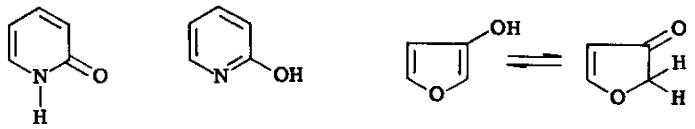
[*11*] [*12*] [*13*]

(*vi*) Annular carbon and nitrogen atoms (cf. **14**⇌**15**),



[*14*] [*15*]

Types *i* and *ii* are the most important. An essential difference between them is that in type *i* both tautomers can be aromatic [e.g., pyrid-2-one (**16**) and 2-hydroxypyridine (**17**) both satisfy the criteria for aromaticity[11] and have large resonance energies], whereas in type *ii* at least one tautomer, that corresponding to **3**, is nonaromatic [e.g., 3-hydroxyfuran (**18**) is aromatic, but furan-3-one (**19**) is not]. In



[*16*] [*17*] [*18*] [*19*]

general, tautomerism of type *i* is important for six-membered heterocycles containing at least one annular nitrogen atom, such as pyridines and azines, whereas type *ii* is important for five-membered heterocycles with one annular hetero atom, e.g., pyrroles, furans, and thiophenes. Tautomerism of both types *i* and *ii* is important for five-membered rings containing two or more annular hetero atoms.

Tautomerism of types *iii–vi* occurs less frequently than of types *i* and *ii*. As a general rule, both tautomeric structures in types *iii* and *iv*, but neither structure in type *v*, and only one in type *vi*, will be aromatic. Type *v* does not fall strictly within the scope of this review, but it is included because both of these structures can be tautomeric with a third form which is aromatic; e.g., **12** and **13** can be in equilibrium with **11**.

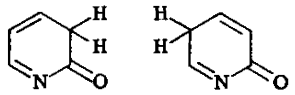
B. Nomenclature

The naming of compounds in which the ring carries hydroxyl, mercapto, amino, and similar groups presents no difficulties, and the recognized conventions of *Chemical Abstracts* are followed. However, there is much confusion in the naming of compounds containing annular carbonyl, thiocarbonyl, imino, or similar groups. In this chapter and in the following three chapters, the ring carbonyl, thiocarbonyl, and imino groups are denoted by the suffixes -one, -thione, and -onimine, respectively, and their position in the ring is indicated by a numeral placed immediately before the suffix, for example, -2-one and -3-thione.[13] Compounds containing these annular groups can be named either as derivatives of the parent aromatic system or as dihydro derivatives; thus, compound **16** could be named pyrid-**2**-one or 1,2-dihydropyrid-2-one and compound **19**, furan-3-one or 2,3-dihydrofuran-3-one (see discussion in reference 14). Both systems of nomenclature have their advantages and disadvantages; the former system is used here which means that the position of the "extra hydrogen" attached to the annular atom is not defined. However, this position is often unambiguous (e.g., in **19**) or the alternative struc-

[13] An alternative convention, which is used by *Chemical Abstracts*, indicates both the position of substitution and the postion of the "extra hydrogen" atom immediately before the name of the parent compound, e.g., 2(1*H*)-pyridone. The prefix "keto" has been used in the literature to designate a cyclic carbonyl group, but this usage has a distinct disadvantage since it implies that the carbonyl group has ketonic properties which is often not the case.

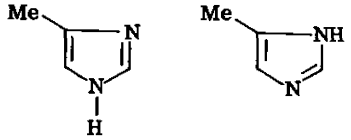
[14] Handbook for Chemical Society Authors, *Chem. Soc. (London), Spec. Publ. No.* **14**, pp. 197–198 (1960).

tures (e.g., pyrid-2-one could describe **20** or **21** as well as **16**) are very



[20] [21]

improbable. In cases where the position of the extra hydrogen atom must be defined, the method used is illustrated by the names given to structures **12** and **13**, i.e., 3*H*-furan-2-one and 5*H*-furan-2-one, respectively.



[22] [23]

The same system of nomenclature can be used to differentiate tautomers of types **22** and **23**, which would be named 4-methyl-1*H*-imidazole and 4-methyl-3*H*-imidazole, respectively.

C. The Existence of Individual Tautomers

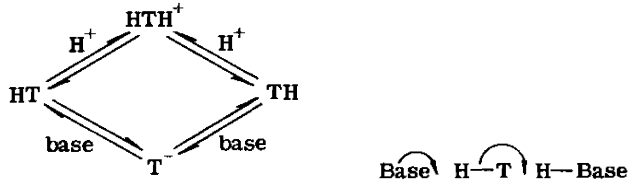
The concept of "mesohydric tautomerism" was advanced by Hunter and his associates in a series of papers which appeared between 1940 and 1950 (e.g., references 15 and 16). This concept was based on the fact that in all cases where the mobile hydrogen atom would be bonded to oxygen, sulfur, or nitrogen atoms in both possible tautomers, the individual forms had not been isolated. It was further established that many of these compounds were associated both in the liquid state and in solution, and it was concluded that the individual tautomers did not exist. The actual molecules were thought to be intermolecularly hydrogen-bonded, the mobile hydrogen atom being bonded equally to both of the hetero atoms. This concept has been useful and has led to clarification of the tautomerism which occurs in solids and

[15] L. Hunter, *J. Chem. Soc.* p. 806 (1945).
[16] L. Hunter and N. G. Reynolds, *J. Chem. Soc.* 2857 (1950).

liquids (obviously the concept cannot be applied to dilute solutions or vapors unless the solute molecules exist as cyclic polymers under these conditions). However, it has been demonstrated recently that hydrogen bonds are usually unsymmetrical, and, therefore, the existence of individual tautomers in the solid and liquid states can be discussed validly. Extensive evidence substantiating the correctness of this conclusion is given in the following three chapters.

D. The Mechanism and Rate of Tautomeric Change

Interconversion between two tautomeric structures can occur via discrete cationic or anionic intermediates (scheme **24**, where "T" is an anion capable of reacting with a proton at a minimum of two distinct sites). Alternatively, interconversion can occur by simultaneous loss and gain of different protons (scheme **25**, where "T" has the same definition as in scheme **24**).[17] These mechanisms are well established for acyclic compounds,[3] but they have been much less thoroughly investigated for heteroaromatic systems. The rate of interconversion of two tautomers is greatest when both of the alternative atoms to which the mobile proton can be attached are hetero atoms, and isolation of the separate isomers is usually impossible in this case. If one of the alternative atoms involved in the tautomerization is carbon, the rate of interconversion is somewhat slower, but still fast. When both of the atoms in question are carbon, however, interconversion is



[24] [25]

usually comparatively slow and requires a catalyst. The tautomerism encountered in the majority of heterocyclic systems is of the first or

[17] An intramolecular photochemical proton-transfer mechanism has also been postulated by W. C. Clark and G. F. Lothian [*Trans. Faraday Soc.* **54**, 1790 (1958)].

second of these types, and, in general, little else is known about interconversion rates except that they are fast.[18]

Up to the present the principal interest in heteroaromatic tautomeric systems has been the determination of the position of equilibrium, although methods for studying fast proton-transfer reactions (e.g., fluorescence spectroscopy[19] and proton resonance[20]) are now becoming available, and more interest is being shown in reactions of this type (see, e.g., references 21 and 22 and the references therein). Thus, the reactions of the imidazolium cation and imidazole with hydroxyl and hydrogen ions, respectively, have recently been demonstrated to be diffusion controlled.[23]

E. Influence of External Factors on the Equilibrium Position of a Tautomeric Mixture

The proportion of any one tautomer present in an equilibrium mixture can change if a change in environment alters the relative stabilities of the isomers by preferentially stabilizing one of them. If one isomer is more polar than another, it will be preferentially stabilized in media with high dielectric constants; e.g., it will be more stable in water than in a hydrocarbon solvent. Specific interaction with the solvent, in particular hydrogen bonding with the solvent acting as the hydrogen donor, or acceptor, or both, often preferentially stabilizes one isomer. Frequently the preceding types of stabilization occur simultaneously; thus, β-hydroxypyridine exists predominantly as such in nonpolar solvents, whereas in aqueous solution about 50% is in the zwitterion form (see following article II by Katritzky and Lagowski). Preferential stabilization of these types is well known in the keto-enol tautomerism of aliphatic compounds (cf., for example, references 24 and 25).

The composition of an equilibrium mixture can also be temperature dependent; thus, Mason[26] has shown that the concentration of the NH forms of 3-hydroxypyridine, 5-hydroxyquinoline, and 6- and 8-hydroxyisoquinoline present at equilibrium decreases as the temperature rises (see Section II,R, of following article II).

Sheĭnker and Peresleni[26a] have shown that substitution of deuterium for hydrogen has little effect on the tautomeric equilibria in 2-phenylsulfonamidopyridine, 2-trichloroacetamidopyridine, 2-nitramidopyridine, and similar compounds.

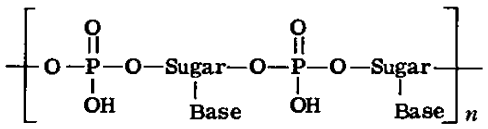
[18] Di-2-quinolylmethane is an exception [G. Scheibe and W. Riess, *Chem. Ber.* **92**, 2189 (1959)]; cf. Section VI,E, in article II by Katritzky and Lagowski.
[19] W. S. Metcalf, *J. Chem. Soc.* p. 3729 (1960).
[20] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance." McGraw-Hill, New York, 1959.
[21] M. Eigen and G. G. Hammes, *J. Am. Chem. Soc.* **82**, 5951 (1960).
[22] M. Eigen and K. Kustin, *J. Am. Chem. Soc.* **82**, 5952 (1960).
[23] M. Eigen, G. G. Hammes, and K. Kustin, *J. Am. Chem. Soc.* **82**, 3482 (1960).
[24] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," p. 103. Clarendon Press, Oxford, 1950.
[25] E. M. Kosower, *J. Am. Chem. Soc.* **80**, 3267 (1958).

F. Importance of the Tautomerism of Heteroaromatic Compounds

Modern concepts have been extended to the chemistry of heterocyclic compounds more slowly than to the chemistry of aromatic and aliphatic systems, but efforts are now being made to classify and explain the properties and reactions of heterocyclic compounds in terms of these newer ideas (cf. reference 11). However, many of the most important heterocyclic compounds are potentially tautomeric, and elucidation of their tautomeric composition must precede a logical treatment of their properties. Further, many natural products such as the nucleic acids and alkaloids contain potentially tautomeric groups and information of this type is needed for a detailed explanation of the reactions which they undergo.

Tautomerism of the heterocyclic bases contained in the nucleic acids has been suggested as a possible explanation for the spontaneous mutation of genes—the basis of evolution.[27,27a] Nucleic acids consist of long sugar-phosphate chains in which each sugar molecule carries a heterocyclic base (cf. **26**). Two nucleic acid molecules are paired in a double helix, the heterocyclic bases of one molecule hydrogen-bonding with those of the other. Cytosine is always bonded with guanine (cf. **27**), and thymine (cf. **28**, R = Me) or uracil (cf. **28**, R = H) always forms hydrogen bonds with adenine (cf. **28**), the tautomeric form of the bases determining the type of hydrogen bonding. During replication of the nucleic acids, the double helix separates, and a new strand is built up on each of the two original strands. In this way two

[26] S. F. Mason, *J. Chem. Soc.* p. 5010 (1957).
[26a] Yu. N. Sheĭnker and E. M. Peresleni, *Stroenie Veshchestva i Spektroskopiya, Akad. Nauk S.S.S.R.* p. 28 (1960); *Chem. Abstr.* **55**, 10067 (1961).
[27] J. D. Watson and F. H. C. Crick, *Cold Spring Harbor Symposia Quant. Biol.* **18**, 123 (1953).
[27a] E. Freese, *J. Mol. Biol.* **1**, 87 (1959).



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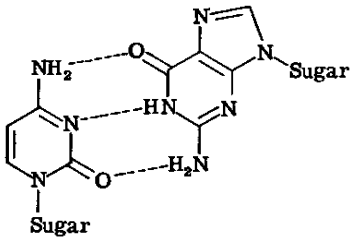

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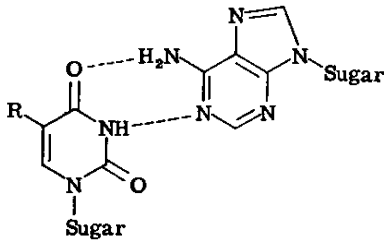

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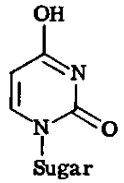


[29]

identical double helices are formed (see, for example, reference 28). The tautomeric form of uracil illustrated by **29** is similar to cytosine, and it has been postulated that if uracil reacts in form **29**, it could pair with guanosine rather than with adenine, this "mistake" being manifested as a spontaneous mutation.[27]

II. Chemical Methods Used to Study Tautomerism

Tautomerism can be studied by various chemical and physical techniques. In principle, it is possible to obtain significant results from chemical evidence, but in practice this is very difficult, and physical methods are much more useful. Chemical methods are discussed first and emphasis is placed on the dangers inherent in their application. It should be emphasized that many of the incorrect conclusions drawn from chemical evidence were made before these dangers had been realized.

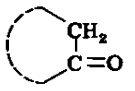
[27] *Chem. Eng. News* **39**, No. 19, 81 (1961).

The chemical methods can be subdivided into two interrelated groups: (*a*) those which depend on the reactivity of a particular structural feature, e.g., a carbon-carbon double bond or an enolic hydroxyl group, that is present in only one of the tautomeric forms; and (*b*) those which involve relating the structures of reaction products to the structures of the starting materials.

A. Chemical Reactivity

Methods of the first type have been used for both qualitative and quantitative investigation. An important limitation is that the rates of interconversion of the tautomeric forms must be small as compared with those of the test reaction(s). The method is further complicated since the test reactions are sometimes complex and it is difficult to be certain that only one tautomer is reacting. An even more fundamental objection is that much chemical evidence is based on incorrect reaction mechanisms. Thus, the formation of condensation products (**30**) with aldehydes has repeatedly been quoted as evidence *for* structures of type **31** and *against* type **32**, whereas if **31** does react with an aldehyde it must either first tautomerize to **32** or ionize to **33**.

[30]



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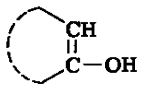

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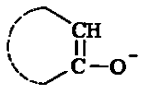


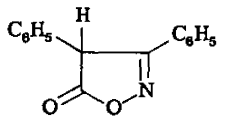
[33]

Bromine titration[29] has been applied to several heteroaromatic compounds, but it is not a reliable method. The assumption is often made that oxo structures react very slowly with bromine whereas the hydroxy forms react rapidly. Thus, 3,4-diphenylisoxazol-5-one when freshly dissolved in ethanol was found to react with 0.5 mole of bromine, but after standing it reacted with almost 1 mole. These observations led to the conclusion[30] that the solid was in the CH

[29] K. H. Meyer, *Ann. Chem. Liebigs* **380**, 212 (1911).

[30] E. P. Kohler and A. H. Blatt, *J. Am. Chem. Soc.* **50**, 504 (1928).

form (34) (which has since been disproved; see p. 475) but that the OH form (35) predominated in solution (also unlikely). Facts such as the rapid reaction of 3-phenylisoxazol-5-one with 1.9 moles of bromine[31] also undermine confidence in the bromine titration method.



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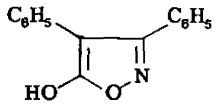
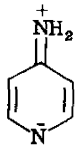


[35]

Compounds containing a reasonable proportion of an enolic hydroxyl group, i.e., C=C—OH, usually give a deep color with ferric chloride, and this has often been used as a qualitative test. In this way, 2-hydroxythiophene has been shown to exist, at least in part, in the hydroxy form.[32]

The observations that heteroaromatic amino compounds are not easily diazotized, are quite readily hydrolyzed,[33-35] and often do not form Schiff bases with aldehydes[36,37] have all been incorrectly interpreted as indications that these compounds exist principally in the imino form, whereas these observations can reasonably be attributed to the fact that the amino groups in compounds of the type of 4-aminopyridine are electron deficient as a result of the contribution of structures of type 36.[38]

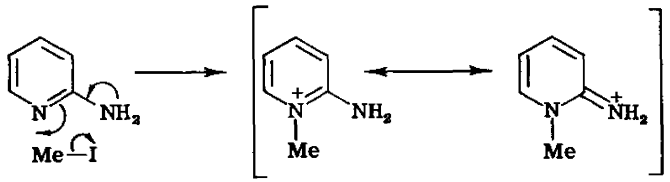


[36]

[31] C. L. Angyal and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 2181 (1953).
[32] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.* **72**, 5543 (1950).
[33] G. T. Morgan and L. P. Walls, *J. Chem. Soc.* p. 2225 (1932).
[34] J. R. Marshall and J. Walker, *J. Chem. Soc.* p. 1004 (1951).
[35] R. R. Goodall and W. O. Kermack, *J. Chem. Soc.* p. 1546 (1936).
[36] A. Albert and B. Ritchie, *J. Chem. Soc.* p. 458 (1943).
[37] J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.* p. 571 (1943).
[38] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.* p. 1461 (1952).

B. Product Structure

The second group of chemical methods is based on a comparison of the structure(s) of the reaction product(s) with that of the starting material. These methods can be illustrated by the observation that 1-methylpyrid-2-onimine (38) is formed when 2-aminopyridine (37) is allowed to react with methyl iodide followed by treatment with alkali. From these data it was incorrectly concluded that 2-aminopyridine reacted, or existed, in the imino form.[39,40] Actually, the



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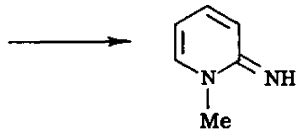


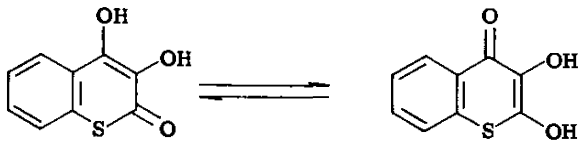
[38]

[39] [40]

orientation of the alkyl groups shows that the compound reacts in the *amino form*, indicating that at least part of it exists in this form. Under strongly basic conditions, alkylation of compounds of the type illustrated by 2-aminopyridine occurs on the amino-nitrogen atom; it is probably the mesomeric anion 39 ↔ 40 which undergoes reaction (cf. detailed discussion in reference 11, pp. 93–94).

[39] A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber. deut. chem. Ges.* **54**, 814 (1921).
[40] E. A. Steck and G. W. Ewing, *J. Am. Chem. Soc.* **70**, 3397 (1948).

Identification of the product(s) resulting from the reaction of heterocyclic compounds with diazomethane has been used in attempts to elucidate their tautomeric composition (for summaries, see references 7 and 41). This work was based on the assumption that if a compound which is capable of existing in both an =NH and an —OH form produced only the =NMe derivative when it was treated with diazomethane, it existed entirely in the =NH form. On the other hand, formation of the —OMe derivative was interpreted to mean that a finite amount of the compound existed in the —OH form. In some cases the tautomer present in the solid state was concluded to be different from that present in solution; for example, **41** ⇌ **42** gave a higher proportion of the 3,4-dimethoxy derivative when ethereal diaz-



[*41*] [*42*]

omethane was added to the solid substance at once than when it was added slowly[42,43] (see also the discussion of triazinones in Section II,T, of the following article II by Katritzky and Lagowski).

The whole concept of "direct" methylation has recently been critically reviewed and rejected by Gompper[44,44a] as a method to study tautomerism. The difference in the proportions of the two methyl derivatives produced when diazomethane is in excess, or the reverse, has now been ascribed to the relative importance of the S_N and S_{N^2} reactions of the tautomeric compound with diazomethane. The proportions of *N*- and *O*-methyl derivatives formed by the reaction of cyclic amides with diazomethane has been related to the infrared ν C=O frequencies.[45]

[41] F. Arndt, *Angew. Chem.* **61**, 397 (1949).
[42] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **62**, 36 (1929).
[43] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **68**, 1572 (1935).
[44] R. Gompper, *Chem. Ber.* **93**, 187 (1960).
[44a] F. Arndt, B. Eistert, R. Gompper, and W. Walter, *Chem. Ber.* **94**, 2125 (1961).
[45] R. Gompper, *Chem. Ber.* **93**, 198 (1960).

III. Physical Methods Used to Study Tautomerism

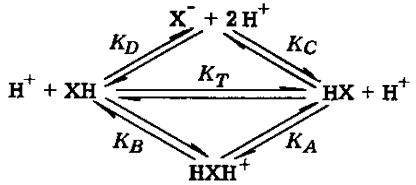
In general, physical methods have been used to study tautomerism more successfully than chemical methods, and, of the physical methods, those involving measurements of basicities and ultraviolet spectra are the most important, followed by those involving measurement of infrared and proton resonance spectra. An attempt is made here to delineate the scope and to indicate the advantages and disadvantages of the various methods. A short review by Mason[46] of the application of spectroscopic methods appeared in 1955. Recently a set of reviews[46a] on the applications of physical methods to heterocyclic chemistry has appeared, which treats incidentally the determination of tautomeric structure.

A. Basicity Measurements[46b,46c]

The determination of pK_a values is probably the most generally useful method for the investigation of tautomerism. This method was first employed in the heterocyclic field in the early 1950's by Tucker and Irvin[47] and by Angyal and Angyal.[38] There are two empirical dissociation constants, K_1 and K_2, for the conjugate acid (HXH^+) of a tautomeric compound. Constants K_1 and K_2 are, in effect, a summation of the true dissociation constants K_A, K_B, K_C, and K_D of the individual tautomeric forms (see scheme **43**, where XH and HX are tautomers) and the tautomeric constant, K_T; these constants are related by the following equations:

$$K_1 = K_A + K_B$$
$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D}$$
$$K_T = K_A/K_B = K_C/K_D$$

[46] S. F. Mason, *Chem. Soc. (London), Spec. Publ. No.* **3**, p. 139 (1955).
[46a] A. R. Katritzky (ed.), "Physical Methods in Heterocyclic Chemistry." Academic Press, New York, 1962.
[46b] A. Albert and E. Serjeant, "Ionisation Constants, a Laboratory Manual." Methuen, London, 1962.
[46c] A. Albert, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 1. Academic Press, New York, 1962.
[47] G. F. Tucker, Jr., and J. L. Irvin, *J. Am. Chem. Soc.* **73**, 1923 (1951).



[43]

Replacement of a hydrogen atom by an alkyl group such as a methyl group usually has no effect, or only a very small effect, on the ionization constant; thus, the ionization constant of $HXMe^+$ is approximately equal to K_B and that of $MeXH^+$ to K_A. Therefore,

$$K_T = \frac{K_{(HXMe^+)}}{K_1} - 1 = \frac{K_1}{K_{(MeXH^+)} - K_1}.$$

It follows that K_T can be theoretically calculated from K_1 and the ionization constant of either of the alkylated derivatives. In practice, however, this can only be done if there is an appreciable difference between the constant for the alkylated derivative and the value of K_1. Mason[48] has argued that it is better to use the ionization constants of both alkylated forms in the equation $K_T = K_{(MeXH^+)}/K_{(HXMe^+)}$, for in this case the errors introduced by assuming that $K_{(MeXH^+)} = K_A$, etc., may well partially cancel. However, methyl groups can be base-weakening as well as base-strengthening; the data shown in Table I indicate that the base-weakening inductive

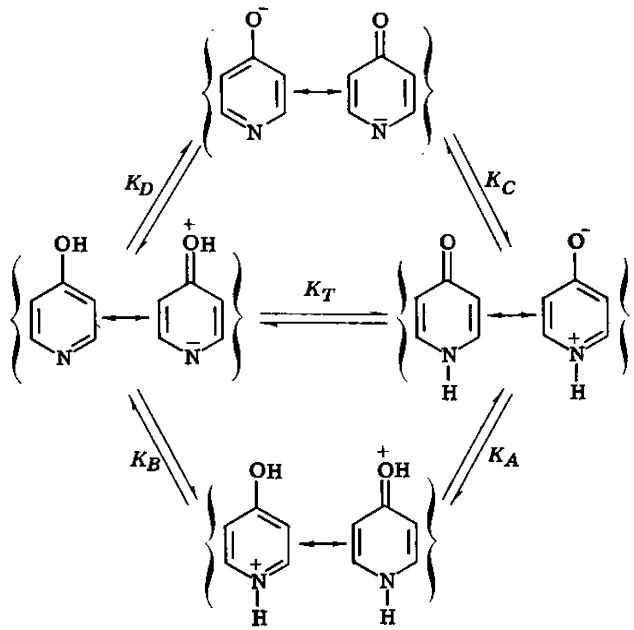
TABLE I
pK_a VALUES OF SOME SUBSTITUTED ANILINES

Compound	*Ortho*	*Meta*	*Para*
Methoxyanilines	4.49	4.20	5.29
Hydroxyanilines	4.72	4.17	5.50

effect is very similar for hydroxyl and methoxyl groups but that the base-strengthening mesomeric effect is somewhat stronger for hydroxyl groups (cf. reference 49). Individual cases are best considered on their own merits.

[48] S. F. Mason, *J. Chem. Soc.* p. 674 (1958).
[49] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).

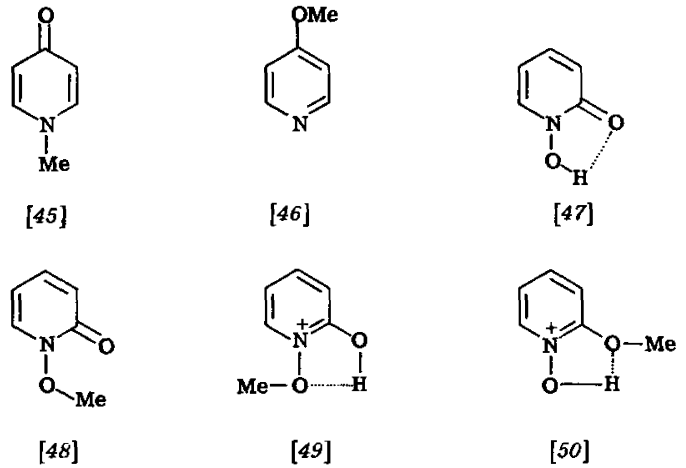
To illustrate the elucidation of tautomeric equilibria using basicity measurements, the following data for pyrid-4-one[49] may be con-



[44]

sidered (see scheme 44). The experimentally determined value for pK_1 is 3.27 and that for pK_2 is 11.09; the pK_a values of the methylated compounds **45** and **46** are 3.33 and 6.62, respectively. Using these values, it can be shown that $pK_T = 3.29$, $pK_A = 3.27$, $pK_B = 6.56$, $pK_C = 11.09$, and $pK_D = 7.80$.

The foregoing assumption that alkylation does not affect pK_a values, which can be tested, is generally true to within ca. 0.3 pK units. Sometimes alkylation breaks a strong hydrogen bond (cf. **47**, **48**), and then the basicity of the alkylated and nonalkylated forms can differ considerably (for compound **47**, by 0.5 to 0.9 pK units). Another implied assumption in this method is that the structures of the cations formed by the potentially tautomeric compound and both alkylated forms are similar, which is not always true (cf. **49**, **50**). In these cases the method is not reliable.



[45] [46] [47]

[48] [49] [50]

B. Ultraviolet Spectroscopy[50]

The electronic spectrum of a compound arises from its π-electron system which, to a first approximation, is unaffected by substitution of an alkyl group for a hydrogen atom. Thus, comparison of the ultraviolet spectrum of a potentially tautomeric compound with the spectra of both alkylated forms often indicates which tautomer predominates. For example, Fig. 1 shows that 4-mercaptopyridine exists predominantly as pyrid-4-thione. In favorable cases, i.e., when the spectra of the two alkylated forms are very different and/or there are appreciable amounts of both forms present at equilibrium, the tautomeric constant can be evaluated. By using this method, it was shown, for example, that 6-hydroxyquinoline exists essentially as such in ethanol but that it is in equilibrium with about 1% of the zwitterion form in aqueous solution[26] (Fig. 2).

This method is not applicable if the spectra of the potentially tautomeric compound and both alkylated derivatives are very similar, e.g., it is not suited to an investigation of the tautomerism of 4-aminopyridine 1-oxide (Fig. 3). A further limitation is that often only qualitative conclusions can be drawn because no contribution from the spectrum of the minor constituent can be found in the spectrum of the tautomeric compound. It should also be noted that, un-

[50] Cf. S. F. Mason, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 7. Academic Press, New York, 1962.

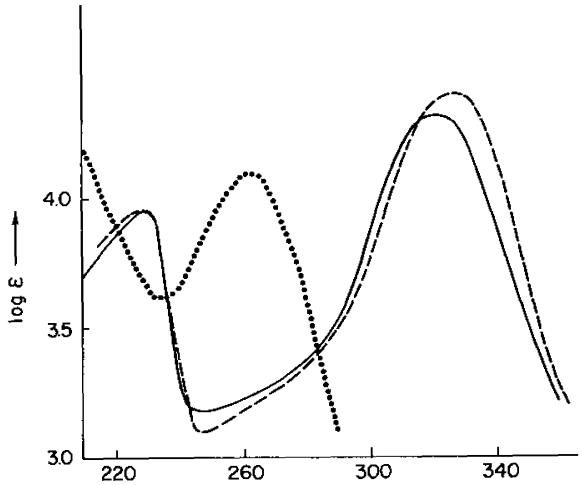


Fig. 1. Spectrum of pyrid-4-thione (————), 1-methylpyrid-4-thione (— — — — —), 4-benzylthiopyridine (.....). [Cf. A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 3160 (1958).]

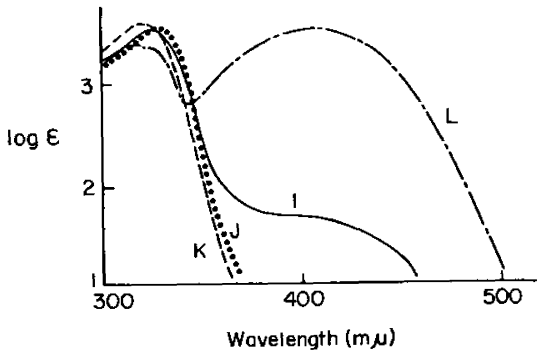


Fig. 2. Spectrum of 6-hydroxyquinoline in aqueous buffer (————), 6-methoxyquinoline (— — — — —), anhydro-6-hydroxy-1-methylquinolinium hydroxide (— · — · — ·), 6-hydroxyquinoline in aqueous buffer (.....). [From S. F. Mason, *J. Chem. Soc.* p. 5010 (1957), by permission of The Chemical Society.]

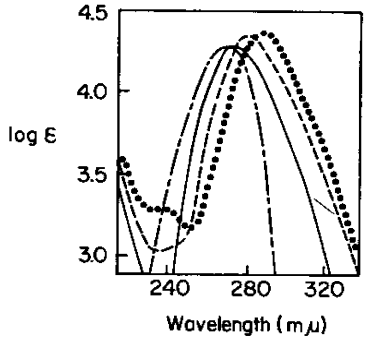


FIG. 3. Spectrum of 4-aminopyridine 1-oxide (————), 4-methylaminopyridine 1-oxide (— — — — —), 4-dimethylaminopyridine 1-oxide (.....), 1-methoxypyrid-4-onimine (— · — · — ·). [From J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* p. 4375 (1957), by permission of The Chemical Society.]

less both reference compounds are studied, the conclusions can be erroneous; thus, for example, the imino structure was incorrectly assigned to amino-pyridines, -quinolines,[40] and -cinnolines[51] (these cases are discussed in the following article).

C. Infrared Spectroscopy[52]

Many of the groups occurring in potentially tautomeric heteroaromatic compounds give rise to characteristic infrared absorption bands, e.g., $-NH_2$, —OH, —SH, =C=O, and =C=S groups. The presence or absence of such bands is a criterion for the structure of a particular compound; many examples of the application of criteria of this type to studies of tautomerism are given in the following three articles. Within recent years the vibrational modes of heterocyclic nuclei and their associated infrared absorption bands have received considerable attention (for reviews, see references 52 and 53). It is now possible, for an ever increasing number of compounds, to identify with a fair degree of certainty those bands in a spectrum

[51] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.* p. 3318 (1951).

[52] Cf. A. R. Katritzky and A. P. Ambler, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 10. Academic Press, New York, 1962.

[53] A. R. Katritzky, *Quart. Revs.* 13, 353 (1959).

that are produced by the heterocyclic nuclei; the bands remaining are attributed to and also characteristic of the substituent(s). As an example, Table II gives a complete assignment for the important

TABLE II
INFRARED BANDS AND ASSIGNMENTS FOR 2-ACETAMIDOPYRIDINE[a]

Band (cm^{-1})	ϵ_A	Assignment
3410	40	ν NH, free
3018[b]	25	ν NH, H-bonded
2890	50	ν CH, hydrogen bonded $CHCl_3$
1694	255	ν C=O
1600	120	A_1 ring stretch
1580	220	B_1 ring stretch
1527[b]	120	Amide II band
1508	290	Amide II band
1460	60	A_1 ring stretch
1434	325	B_1 ring stretch
1400[b]	35	Acetamido ?
1367	80	CH_3, s-bend
1300	350	ν C–N
1280	25	A_1 BCH
1149	60	A_1 BCH
1092	10	B_1 BCH
1050	20	A_1 BCH
1035[b]	15	?
1000	30	γ CH
961	15	CH_3 rock

[a] Data taken from A. R. Katritzky and A. R. Hands, *J. Chem. Soc.* p. 2202 (1958) and from A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2067 (1959).

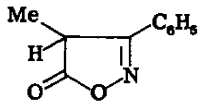
[b] Shoulder.

bands of 2-acetamidopyridine in the region 3800–800 cm^{-1} and provides strong evidence that this compound exists predominantly in the amino form. In favorable cases, bands due to individual tautomers in a mixture can be identified. Table III gives the bands observed for 4-methyl-3-phenylisoxazol-5-one in chloroform and their assignment to the individual tautomers; comparison of ϵ_A values with those observed for compounds of fixed structure shows that the ratio of **51** to **52** is about 2:1 in this solvent.

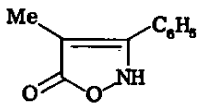
TABLE III
INFRARED BANDS AND ASSIGNMENTS FOR 4-METHYL-3-PHENYLISOXAZOL-5-ONE[a]

Band (cm^{-1})	ϵ_A	Structure	Assignment
1800	370	**51**	ν C=O
1735	240	**52**	ν C=O
1639	70	**52**	ν C=C
1600	15	**52**	Ph, ν C—C
1579	10	**52**	Ph, ν C—C
1553	25	**51**	Ph, ν C—C
1502	15	**51** + **52**	Ph, ν C—C
1453	60	**51** + **52**	Ph, ν C—C
1410	25	**52**	Me, CH def.
1387	50	**52**	Me, CH def.
1364	25	**52**	Isoxazolone ring
1264	35	**52**	Isoxazolone ring
1168	100	**51**	Isoxazolone ring
1101	15	**51**	?
1091	20	**51**	CH_3 rocking
1062	50	**52**	Isoxazolone ring
1038	40	**51**	Isoxazolone ring
1021	30	**52**	Ph, β CH
1000	55	**52**	?
990	60	**52**	?
918	10	**51**	Ph
883	270	**51**	Isoxazolone ring

[a] Data taken from A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).



[*51*]



[*52*]

D. X-RAY CRYSTALLOGRAPHIC STUDIES[54]

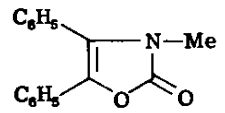
X-Ray crystallographic studies of solid compounds have been used to infer the position in the structure of potentially tautomeric hydrogen atoms. These positions are either found directly by high precision techniques or deduced from the lengths of the other bonds in the molecule.

The determination of the structure of adenine hydrochloride (see Volume 2, Section IV,K, of article IV by Katritzky and Lagowski) is an example of extremely accurate X-ray crystallography whereby the positions of individual hydrogen atoms were located. An example of the deduction of structure from bond lengths between "heavy" atoms is provided by Penfold's investigation of pyrid-2-thione.[55]

[54] Cf. W. Cochran, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 3. Academic Press, New York, 1962.

E. FLUORESCENCE SPECTROSCOPY

If the ultraviolet spectra of a potentially tautomeric compound and of both alkylated derivatives are too similar to allow conclusions to be drawn regarding their structures, sometimes fluorescence spectra can be used instead. By using this technique, Gompper and Herlinger[56] showed that 4,5-diphenyloxazol-2-one (**53**) does, indeed, exist in the 2-oxo form.



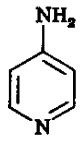
[*53*]

F. DIPOLE MOMENTS[57]

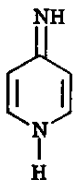
Dipole moment data have provided valuable information for the study of the tautomerism of compounds such as isonicotinic acid,[58] pyrid-4-one,[58] and ethyl acetoacetate.[59] However, this method must be used with discretion since it can lead to inconclusive results. Thus, the fact that 4-aminopyridine has a higher dipole moment than the algebraic sum of the dipole moments of pyridine and aniline was originally interpreted as proof that structure **54** exists with a strong contribution from **36**, and it was stated that **55** would have a very low moment.[58] Later, Angyal and Angyal[38] pointed out that the

[55] B. R. Penfold, *Acta Cryst.* **6**, 707 (1953).
[56] R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2816 (1956).
[57] Cf. S. Walker, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 5. Academic Press, New York, 1962.
[58] D. G. Leis and B. C. Curran, *J. Am. Chem. Soc.* **67**, 79 (1945).
[59] R. J. W. LeFèvre and H. Welsh, *J. Chem. Soc.* p. 1909 (1949).

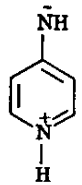
imino form **55** would also be expected to have a high dipole moment as a result of the contribution from **56**.



[54]



[55]



[56]

G. Polarographic Techniques[60]

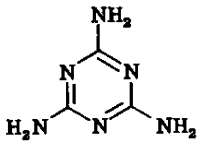
Polarographic techniques have been used by Sturm and Hans[61] to demonstrate that certain amino-thiadiazoles and -benzthiazoles exist in the amino form (cf. also references 62, 63). This method, which involves comparison of the polarographic rdeuction potentials of the potentially tautomeric substance with those of alkylated reference compounds, has not been applied often, but may well prove to be a means to obtain qualitative information quickly. There is a possibility that the method can be modified to yield quantitative data.[61]

H. Molecular Orbital Calculations

Molecular orbital calculations have been used to estimate equilibrium constants, although up to the present these attempts have not met with much success. Using calculations of this type, 2- and 4-hydroxypyridine 1-oxide were predicted to be more stable than 1-hydroxypyrid-2- and -4-one by ca. 20 kcal/mole, which corresponds to a ratio of ca. 10^{14} between the forms.[64] It was later shown experimentally that, at least in the series of 4-substituted compounds, there is very little energy difference between the forms and that the ratio between them is about unity.[64a] Molecular orbital calculations for

[60] Cf. J. Volke, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 6. Academic Press, New York, 1962.
[61] F. von Sturm and W. Hans, *Angew. Chem.* **67**, 743 (1955).
[62] J. Goerdeler, A. Huppertz, and K. Wember, *Chem. Ber.* **87**, 68 (1954).
[63] E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. chim. ital.* **88**, 812 (1958).
[64] H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4448 (1955).
[64a] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* p. 4375 (1957).

melamine support the triamino (**57**) rather than the triimino (**58**) formulation[65]; however, no intermediate structures were considered (see following article II, Section IV,F).



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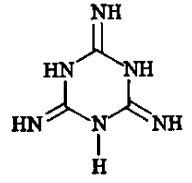


[58]

I. The Hammett Equation

If the basicities of a series of substituted heterocyclic compounds can be correlated by the Hammett equation, the intrinsic basicities of other substituted compounds in that series can be calculated from their σ constants.[66] Thus, for example, the basicities that amino and hydroxyl compounds would exhibit, if they existed as such, can be determined and compared with the actual basicities measured. Unfortunately, these are just the conditions under which the concept of the σ constant tends to break down because hydroxyl and amino groups are strong electron donors and proton addition is a strongly electron-demanding reaction. Calculated intrinsic pK_a values of 1.68 and 2.22 for 4-hydroxy- and 4-amino-pyridine 1-oxide, respectively, were thought to be too low because of the uncertainties in the σ constants.[66] The actual measured values for these compounds were 2.36 and 3.65,[67] respectively, and these data were interpreted to mean that 4-aminopyridine 1-oxide existed either essentially completely as such or, less probably, in equilibrium with 1-hydroxypyrid-4-onimine and that 4-hydroxypyridine 1-oxide existed as such.[66] The authors of this chapter do not feel that in this particular case these conclusions are convincing (see discussion in Section II,F, of article II). The pK_a of the other possible tautomer should certainly be known when this method is used; the Hammett equation essentially provides a way of measuring the pK_a of one tautomeric form without isolating it or using a model. This method has been successfully applied by

[65] M. J. S. Dewar and L. Paoloni, *Trans. Faraday Soc.* **53**, 261 (1957).
[66] H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4445 (1955).
[67] H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.* **77**, 4441 (1955).

Jaffé[66] to pyridine-3- and -4-carboxylic acids and to 3-hydroxypyridine for which values of the σ constants are much more certain.

Another application of the Hammett equation has been discovered recently by a Russian group.[68] For a series of related compounds, a plot of the measured pK_a values against the σ constants of the substituent(s) is a straight line if the form predominating is the same throughout the series. However, if the form predominating changes, two straight lines intersecting at the change-over point will be obtained. The value of K_T for the individual compounds can be obtained from these results.

J. Nuclear Magnetic Resonance Spectroscopy[68a]

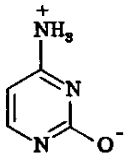
The nuclear magnetic resonance spectrum of a tautomeric compound, either alone or in comparison with those of alkylated derivatives of its alternative forms, can give structural information. Nuclear magnetic resonance spectroscopy has been applied to the investigation of keto-enol tautomerism in aliphatic compounds (see, e.g., reference 69). Thus, under normal conditions the exchange rate of the tautomers of acetylacetone is sufficiently slow so that distinct nuclear magnetic resonance spectra are shown by both forms, thereby enabling the concentration of each tautomer to be measured. The rate of exchange is accelerated by catalysts such as diethylamine, in which case an "average" spectrum is measured.

Hoffman and Gronowitz[70,71] have applied this technique with marked success to the study of hydroxy-, amino-, and mercaptothiophenes. Similarly, it has been shown that pyrid-4-one exists predominantly as such and that 4-hydroxypyridine 1-oxide is in equilibrium with comparable amounts of 1-hydroxypyrid-4-one.[72] The method has also been used to investigate the structure of ions (see Section II,C, of article II by Katritzky and Lagowski).

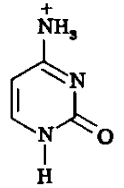
Considerable care must be exercised in the application of proton

[68] M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov, and T. A. Melentyeva, *Tetrahedron* **9**, 10 (1960).
[68a] Cf. R. White, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 9. Academic Press, New York, 1962.
[69] L. W. Reeves and W. G. Schneider, *Can. J. Chem.* **36**, 793 (1958).
[70] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 515 (1961).
[71] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1961).
[72] R. A. Y. Jones, A. R. Katritzky, and J. M. Lagowski, *Chem. & Ind. (London)* p. 870 (1960).

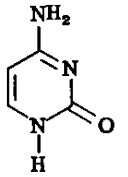
resonance spectroscopy, especially when the alkylated model compounds are not available, since fast proton exchange can simplify a spectrum and cause incorrect conclusions to be drawn. Thus, it has been shown[72a] that the assignment[72b] of the incorrect structures **59** and **60** to cytosine and its cation resulted from the neglect of fast proton exchange in these species. The correct structures are **61** and **62**, respectively.[72a,72c]



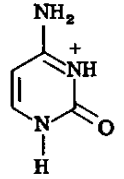
[59]



[60]



[61]



[62]

K. Refractive Index

If the refractivity of the pure tautomeric constituents is known, the composition of the equilibrium mixture can be determined. This method has been used to study, for example, the keto and enol tautomers of ethyl acetoacetate.[73] So far it has not been applied to heterocyclic compounds; in this series the isolation of the pure

[72a] A. R. Katritzky and A. J. Waring, *Chem. & Ind. (London)*, p. 695 (1962).
[72b] J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.* **83**, 2909 (1961).
[72c] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, in press.
[73] L. Knorr, *Ber. deut. chem. Ges.* **44**, 1138 (1911).

tautomers is not usually possible and other procedures are more satisfactory.[74]

L. Molar Refractivity

Molar refractivity is an additive property, and the predominant tautomer can be found by comparing the experimentally determined value with that calculated for the alternative forms. For example, Auwers[74] used this method to demonstrate that pyrid-2-one exists as such and not as 2-hydroxypyridine.

M. Optical Rotation

Optical rotation data have been used in two different ways to study tautomerism. The rate of racemization at an optically active carbon atom gives an upper limit for the rate at which the other tautomeric form is produced; rates of halogenation and deuteration can sometimes be used in a similar way.

In the second method, which can be applied to compounds with an optically active center near the potentially tautomeric portion of the molecule, the effect of the isomerization on the optical activity is measured. In favorable cases both the rate of racemization and the equilibrium position can be determined. This method has been used extensively to study the isomerization of sugars and their derivatives (cf. reference 75). It has not been used much to study heteroaromatic compounds, although the very fact that certain compounds have been obtained optically active determines their tautomeric form. For example, oxazol-5-ones have thus been shown to exist in the CH form (see Volume 2, Section II,D,1, of article IV by Katritzky and Lagowski).

N. Other Methods

Techniques such as Raman spectroscopy and the determination of heats of combustion and reaction could possibly be applied to the study of tautomerism, but so far they have not become important.

[74] K. von Auwers, *Ber. deut. chem. Ges.* **63**, 2111 (1930).
[75] J. W. Baker, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.* **125**, 268 (1924).

Prototropic Tautomerism of Heteroaromatic Compounds: II. Six-Membered Rings

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AND

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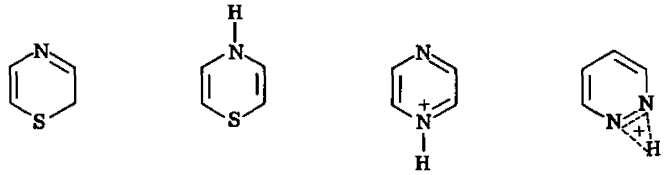
The most important cases of tautomerism in heterocyclic compounds containing six-membered rings involve the movement of a proton between a cyclic nitrogen atom and an atom adjacent to the ring; cf. p. 313. The subject matter presented in this chapter has been subdivided according to the nature of the adjacent atom—oxygen, sulfur, nitrogen, nitrogen carrying various substituents, and carbon are considered successively. Within each of these main sections, a further subdivision has been made according to the number and orientation of cyclic hetero atoms.

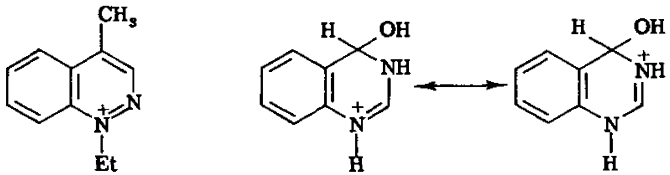
I. Azines and Azine Cations

1,4-Thiazine has been formulated as **1** rather than **2** because it does not form a sulfonamide under Hinsberg conditions.[1] Symmetrical azines can form only one classical monocation, e.g., pyrazine forms **3**. The nonclassical cation **4** has been postulated for pyridazine, but there is no compelling evidence in its favor.



[1] [2] [3] [4]

The reactivity of the methyl group in 4-methylcinnoline ethiodide indicates that the structure of this compound is **5**, and this evidence has also been interpreted to mean that N-1 is the basic group in cinnolines.[2,3] However, evidence of this type is only indicative since the formation of quaternary salts is subject to kinetic control, whereas protonation yields predominantly the thermodynamically more stable cation. The quinazoline cation has been shown to exist in the hydrated, resonance-stabilized form **6**↔**7** by ultraviolet spectroscopy[4] (see Section II,A, of the article by Armarego).



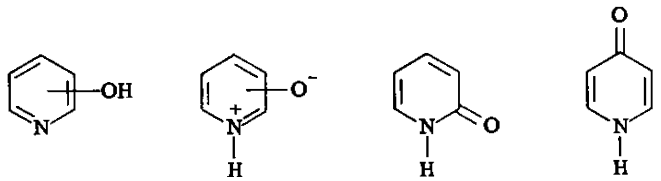
[5] [6] [7]

II. Compounds with Potential Hydroxyl Groups

Hydroxy-pyridines (**8**) and -azines are both weak acids (cf. phe-

[1] C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.* **70**, 684 (1948).
[2] C. M. Atkinson and J. C. E. Simpson, *J. Chem. Soc.* p. 808 (1947).
[3] J. C. E. Simpson, *J. Chem. Soc.* p. 1653 (1947).
[4] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.* p. 4191 (1956).

nols) and bases and can, therefore, exist as zwitterions (**9**). Zwitterions of α- and γ-hydroxy[5] compounds are stabilized by mesomerism with uncharged canonical forms **10** and **11** and thus should be more stable than zwitterions derived from β-hydroxy compounds.

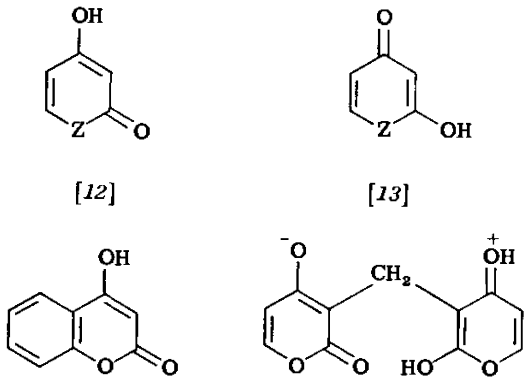


[8] [9] [10] [11]

Heterocyclic compounds carrying potential hydroxyl groups are cyclic amides or vinylogs of amides. There is much physical evidence that acyclic amides exist almost entirely in the oxo form (for references see reference 6), and the apparent contradiction that ultraviolet spectral data appeared to favor the imidol formulation has now been explained on steric grounds.[6] The value of pK_T is estimated to be about 7 on the basis of pK measurements for acyclic amides. Extensive evidence, summarized in the following sections, shows that for α- and γ-hydroxy heterocyclic compounds, the cyclic amide form usually predominates by a substantial factor, often ca. 10^3.

A. Hydroxy-pyranones and -thiapyranones

α,γ-Dihydroxy-pyranones and -thiapyranones can tautomerize to *o*- (**12**, Z = O, S) and *p*-quinonoid forms (**13**, Z = O, S). 4-Hydroxy-6-methylpyran-2-one and 4-hydroxycoumarin (**14**) have been investigated using chemical methods, and from their reaction with diazomethane, the 2-oxo form was concluded to predominate, some of the 4-oxo form being present in solution.[7-9] Both the 2- and the 4-methoxy derivatives of 4-hydroxy-6-methylpyran-2-one[10,11] [see reference 12 for a discussion of the 6-ethyl analog] and 4-hydroxycoumarin[13] have been isolated, and these methylation reactions were discussed in connection with tautomerism. Structure **15** and an analogous structure



[12] [13] [14] [15]

for dicoumarol were proposed on the basis of methylation studies using diazomethane[14]; for further work on the methylation of dicoumarol, see reference 15. The diene system in 4-hydroxy-6-methylpyran-2-one has been reported to undergo Diels-Alder reaction.[16]

Extensive spectroscopic evidence is now available for compounds of the type discussed in this section. The infrared carbonyl frequencies indicate that 4-hydroxy-6-methylpyran-2-one[17] and 2-hydroxy-6-phenylpyran-4-one[18] are the predominating forms in the solid state, but in ethanol the latter changes to 4-hydroxy-6-phenylpyran-2-one

[5] The α and γ are used to denote the position of a substituent relative to a cyclic hetero atom; thus 4-hydroxyisoquinoline is a β-hydroxy compound.

[6] C. A. Grob and B. Fischer, *Helv. Chim. Acta* **38**, 1794 (1955).

[7] F. Arndt, L. Loewe, R. Ün, and E. Ayça, *Chem. Ber.* **84**, 319 (1951).

[8] F. Arndt and S. Avan, *Chem. Ber.* **84**, 343 (1951).

[9] J. Klosa, *Arch. Pharm.* **286**, 37 (1953).

[10] I. Chmielewska and J. Cieślak, *Przemysł. Chem.* **8**, 196 (1952); quoted by H. Nakata, S. Takahashi, K. Yamada, and Y. Hirata, *Tetrahedron Letters* No. 16, p. 9 (1959).

[11] I. Chmielewska, J. Cieślak, and T. Kraczkiewicz, *Roczniki Chem.* **30**, 1009 (1956).

[12] J. Cieślak, S. Lewak, and I. Chmielewska, *Roczniki Chem.* **34**, 423 (1960).

[13] J. Cieślak, *Roczniki Chem.* **26**, 483 (1952).

[14] I. Chmielewska and J. Cieślak, *Tetrahedron* **4**, 135 (1958).

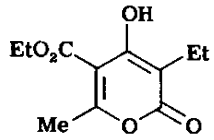
[15] W. Jachymczyk, J. Cieślak, and I. Chmielewska, *Rozniki Chem.* **34**, 925 (1960).

[16] K. Alder and H. F. Rickert, *Ber. deut. chem. Ges.* **70**, 1354 (1937).

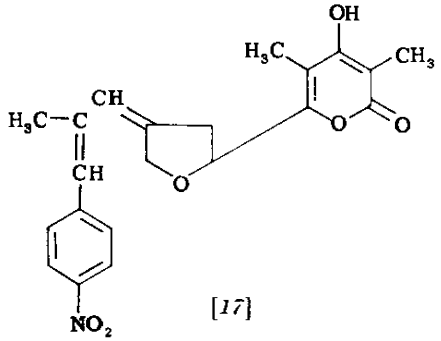
[17] R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.* **78**, 624 (1956).

[18] D. Herbst, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Am. Chem. Soc.* **81**, 2427 (1959).

as evidenced by ultraviolet spectral comparisons.[10,18] The infrared spectrum of **16** in carbon tetrachloride was apparently interpreted to indicate that both the 2-oxo (**16**) and 4-oxo forms are present, but



[16]



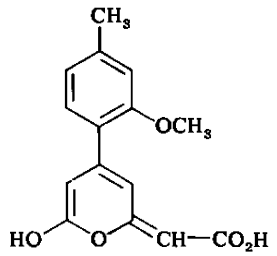
[17]

that the 2-oxo form predominates.[19] An α-pyranone form has been established for desmethylisoaureothin (**17**) on the basis of its ultraviolet spectrum,[20] and the influence of tautomerism on its methylation with diazomethane[20] and dimethyl sulfate[21] has been thoroughly discussed.

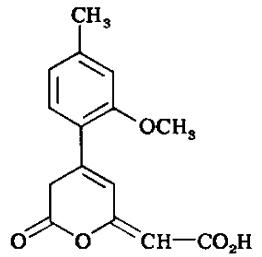
Little is known concerning the tautomerism of glutaric anhydrides and related compounds, although a recent report[22] claims the isolation of the two tautomeric forms (**18** and **19**) of a glutaconic anhydride derivative, which appears improbable.

The large differences between the infrared carbonyl frequencies of

[19] K.-H. Boltze and K. Heidenbluth, *Chem. Ber.* **91**, 2849 (1958).
[20] H. Nakata, *Bull. Chem. Soc. Japan* **33**, 1688 (1960).
[21] H. Nakata, *Bull. Chem. Soc. Japan* **33**, 1693 (1960).
[22] J. J. Nerurkar and V. M. Bhave, *J. Org. Chem.* **25**, 1239 (1960).

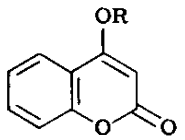


[18]

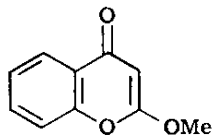


[19]

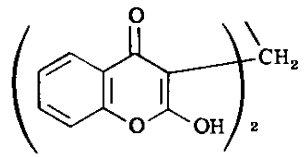
the isomeric methyl derivatives **20** (R = Me) and **21** were used to assign structures to 4-hydroxycoumarin (ν C=O is 1710 cm^{-1} in ethylene dichloride) and dicoumarol (**22**).[23] The infrared spectrum of solid 4-hydroxycoumarin, which showed bands at 1700 and 1673 cm^{-1}, was considered to indicate either that the compound existed in admixture with 2-hydroxychromone *or* that some of the molecules were strongly hydrogen bonded.[24] On the basis of infrared spectral evidence, novobiocine and its hydration product **23** have been assigned 4-hydroxycoumarin structures, but compounds of type **24**,[25] 2,7-dihydroxychromone,[26] and **25**[24] were considered to exist as 2-hydroxychromones. Recently, the infrared spectra of a series of 4-hydroxycoumarins, measured in dioxane solution and as solids, have been discussed in detail with the conclusion being reached that all the 4-hydroxycoumarins (including the 4,7-dihydroxy and 3-piperidinomethyl deriva-



[20]

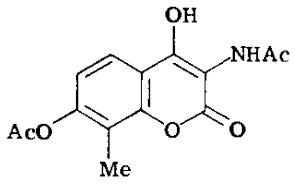


[21]

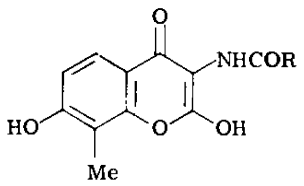


[22]

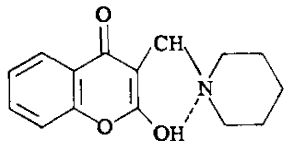
[23] E. Knobloch and Z. Procházka, *Chem. listy* **47**, 1285 (1953).
[24] R. A. Abramovitch and J. R. Gear, *Can. J. Chem.* **36**, 1501 (1958).
[25] C. H. Stammer, E. Walton, A. N. Wilson, R. W. Walker, N. R. Trenner, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.* **80**, 137 (1958).
[26] C. F. Spencer, J. O. Rodin, E. Walton, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.* **80**, 140 (1958).



[23]



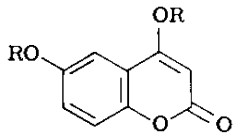
[24]



[25]

tives and dicoumarol, previously formulated as **24**, **25**, and **22**, respectively) exist predominantly in the hydroxycoumarin form.[27]

The ultraviolet spectra provide further evidence for the predominance of the hydroxycoumarin structure. The spectra of 4-hydroxycoumarin (**20**, R = H) and **20** (R = Me) are very similar, indicating that the former exists in the hydroxy form,[28] and this formulation is supported by more recent ultraviolet spectral data.[29] Later, the ultraviolet spectra of **26** (R = H) and **26** (R = Me) were reported to differ, this difference being considered to indicate that 4-hydroxycoumarins exist in a keto form in ethanol[30]; however, this



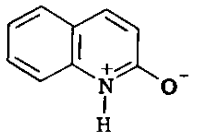
[26]

[27] V. C. Farmer, *Spectrochim. Acta* **10**, 870 (1959).
[28] E. Knobloch, B. Kakáč, and F. Mácha, *Chem. listy* **46**, 416 (1952).
[29] A. Mangini and R. Passerini, *Gazz. chim. ital.* **87**, 243 (1957).
[30] J. F. Garden, N. F. Hayes, and R. H. Thomson, *J. Chem. Soc.* p. 3315 (1956).

divergence was subsequently shown to be the result of partial ionization of **26** (R = H),[31] and the similarity of the absorption spectra of **26** (R = H) and **26** (R = Me) was confirmed.[27]

B. Pyrid-2- and -4-ones (α- and γ-Hydroxypyridines)

It is now well established that α- and γ-hydroxypyridines exist predominantly as pyridones, but in the past there was much discussion concerning the relative importance of these two structure types. In 1905, Meyer[32] suggested that the mobile hydrogen atom was not attached to a definite position in the molecule since acyl derivatives could not be obtained. However, Tschitschibabin and Szokow[33] later reported that acylation of pyrid-2-one gives 2-acetoxypyridine, and on this basis 2-hydroxypyridine was thought to be a tautomeric compound, but no conclusions were drawn regarding the nature of the predominant structure. Pyrid-2-one reacts with diazomethane to give 2-methoxypyridine as the principal product and was concluded to exist as 2-hydroxypyridine by von Pechmann.[34] On reaction with pyrid-4-one, however, diazomethane yields a mixture of products. The tautomerism of 4-hydroxypyridine was discussed in 1930, but no definite conclusions were reached.[35] About this same time the importance of zwitterionic structures was emphasized by Arndt *et al.*[36] (cf. structure **27** for quinol-2-one).

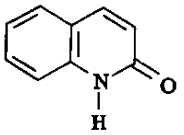


[27]

Ultraviolet spectra have long been used to study systems of this type. In 1889, comparison of the ultraviolet spectrum of 2-hydroxyquinoline with those of its *O*- and *N*-methylated derivatives led

[31] V. C. Farmer and R. H. Thomson, *Chem. & Ind. (London)* p. 112 (1957).
[32] H. Meyer, *Monatsh. Chem.* **26**, 1303 (1905).
[33] A. E. Tschitschibabin and P. G. Szokow, *Ber. deut. chem. Ges.* **58**, 2650 (1925).
[34] H. von Pechmann, *Ber. deut. chem. Ges.* **28**, 1624 (1895).
[35] F. Arndt and A. Kalischek, *Ber. deut. chem. Ges.* **63**, 587 (1930).
[36] F. Arndt, B. Eistert, and W. Ender, *Ber. deut. chem. Ges.* **62**, 44 (1929).

Hartley and Dobbie[37] to conclude that it existed in the oxo form **28**.



[*28*]

Although later investigators showed that the spectral curves originally reported for 2-hydroxyquinoline and its derivatives were inaccurate, the original conclusions were upheld.[38,39] The similarity of the ultraviolet spectra of 4-hydroxypyridine and 1-methylpyrid-4-one was demonstrated in 1907 by Baker and Baly,[40] who concluded that the former existed in the oxo form. The ultraviolet spectrum of 2-hydroxypyridine was also considered to favor the oxo form, although no spectral comparisons with fixed alkylated derivatives were made.[40] The predominance of the oxo forms of 2- and 4-hydroxypyridine, i.e., pyrid-2- and -4-one, was proved conclusively in 1942 by Specker and Gawrosch[41] by comparing the ultraviolet spectra of these compounds with those of their *O*- and *N*-methyl derivatives.

Attempts have been made to deduce the structure of the predominant form of a potentially tautomeric compound from the shifts which occur in the ultraviolet spectrum of the compound in question on passing from neutral to basic or acidic solutions. The fact that no bathochromic shifts were observed for 2- and 4-hydroxyquinoline and 1-hydroxyisoquinoline under these conditions was taken as evidence that they existed in the oxo form[42] [similar work on substituted quinol-4-ones led to no definite conclusions[43]]. A knowledge of the dissociation constants is essential to studies of this type, and the conclusions can, in any case, be only very tentative. A further difficulty encountered in much of the early work is that ionization and tautomerism were not always clearly differentiated.

[37] W. N. Hartley and J. J. Dobbie, *J. Chem. Soc.* **75**, 640 (1899).
[38] R. A. Morton and E. Rogers, *J. Chem. Soc.* **127**, 2698 (1925).
[39] H. Ley and H. Specker, *Ber. deut. chem. Ges.* **72**, 192 (1939).
[40] F. Baker and E. C. C. Baly, *J. Chem. Soc.* **91**, 1122 (1907).
[41] H. Specker and H. Gawrosch, *Ber. deut. chem. Ges.* **75**, 1338 (1942).
[42] G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.* **68**, 2181 (1946).
[43] E. A. Steck, G. W. Ewing, and F. C. Nachod, *J. Am. Chem. Soc.* **71**, 238 (1949).

Recently, many investigators have extended the early observations that the ultraviolet spectra of α- and γ-hydroxypyridines resemble those of their *N*-methyl (not the *O*-methyl) derivatives. This spectral resemblance is found both in aqueous solutions and in solutions of solvents with low dielectric constants, e.g., quinol-4-one in benzene,[44] indicating that these compounds exist predominantly in the oxo form under all conditions. These data are summarized in Table I. In contrast, 4-hydroxyquinoline-3-carboxylic acid has been tentatively concluded to exist in the hydroxy form[45]; pyrid-2-one-4-carboxylic acid has also been formulated as a hydroxy compound,[46] but this has been disputed.[47]

In 1951, Witkop *et al.*[48] interpreted the infrared spectra of quinol-2- and -4-ones to favor the oxo formulation. Since then, many investigators, especially Mason, have reported that potential α- and γ-hydroxy compounds show infrared absorption bands in the ν N—H (3500–3360 cm^{-1}) and ν C=O (1780–1550 cm^{-1})[49] regions of the spectrum and, hence, exist predominantly in the oxo form; references to this work appear in Table I. A study of the bands which occur in the NH-stretching region of the infrared spectra of a series of substituted pyrid-2-ones and quinol-2-ones also supported an oxo formulation for these compounds.[50] Detailed band assignments have been published for pyrid-2- and -4-one.[51,52] Mason[53] has reported that solutions of β-hydroxy compounds in chloroform or carbon tetrachloride show

[44] G. F. Tucker, Jr. and J. L. Irvin, *J. Am. Chem. Soc.* **73**, 1923 (1951).
[45] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.* p. 3318 (1951).
[46] J. Bäumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta* **34**, 496 (1951).
[47] L. Rateb and G. Soliman, *J. Chem. Soc.* p. 1430 (1960).
[48] B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.* **73**, 2641 (1951).
[49] Recent work [A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2947 (1960); L. J. Bellamy and P. E. Rogasch, *Spectrochim. Acta* **16**, 30 (1960)] has shown that the range given earlier for this vibration, 1780–1630 cm^{-1} (reference 53) must be extended. One of the ring vibrations for γ-pyridones absorbs at frequencies higher than ν C=O.
[50] H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **7**, 407 (1959).
[51] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2947 (1960).
[52] A. Albert and E. Spinner, *J. Chem. Soc.* p. 1221 (1960).
[53] S. F. Mason, *J. Chem. Soc.* p. 4874 (1960).

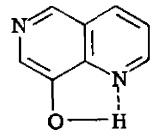
TABLE I

RATIO OF THE OXO FORM TO THE HYDROXY FORM (pK_T) FOR α- AND γ-HYDROXYPYRIDINES

Compound	pK_a Method[a]	pK_a Method[b]	UV Method	IR Method
α-Hydroxy compounds				
Pyrid-2-one	2.5	2.96	pr[d,e]	pr[n,o,p,q,r]
Substituted pyrid-2-ones	—	—	—	pr[s,t,u]
Quinol-2-one	3.5	3.88	pr[f]	pr[o,q,r]
3-Hydroxyquinol-2-one	—	—	pr[g]	—
Isoquinol-1-one	4.3	4.85	—	pr[q]
Substituted isoquinol-1-ones	—	—	pr[h]	—
Phenanthrid-9-one	3.9	—	pr[i]	pr[q]
3-Methyl-2,7-naphthyridin-1-one	—	—	—	pr[v]
1,7-Naphthyridin-8-one	—	—	—	pr[q]
γ-Hydroxy compounds				
Pyrid-4-one	3.3	3.29	pr[e]	pr[n,q,r]
Substituted pyrid-4-ones	—	—	pr[j]	—
Quinol-4-one	4.4	4.19 4.1[c]	pr[c,f,k]	pr[q]
2-Methylbenzo[g]quinol-4-one	—	—	—	pr[q]
6-Nitroquinol-4-one	—	—	pr[k]	—
Ethyl 6,7-dimethoxy-5-methyl-quinol-4-one-2-carboxylate	—	—	—	pr[w]
Pyrazino(4,5-2,3)pyrid-4-one	—	—	—	pr[q]
2-Methyl-1,10-phenanthrol-4-one	—	—	—	pr[q]
Acridan-9-one	7.0	7	pr[l]	pr[r]
Substituted acridan-9-ones	—	—	—	pr[q]
2,6-Diaryl-4-hydroxypyridines	—	—	pr[m]	—

[a] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).
[b] S. F. Mason, *J. Chem. Soc.* p. 674 (1958).
[c] G. F. Tucker, Jr. and J. L. Irvin, *J. Am. Chem. Soc.* **73,** 1923 (1951).
[d] The notation "pr" indicates that the oxo form predominates over the hydroxy form in the equilibrium mixture.
[e] H. Specker and H. Gawrosch, *Ber. deut. chem. Ges.* **75,** 1338 (1942).
[f] R. D. Brown and F. N. Lahey, *Australian J. Sci. Research* **3,** 615 (1950).
[g] R. G. Ault, E. L. Hirst, and R. A. Morton, *J. Chem. Soc.* p. 1653 (1935).
[h] G. Berti and P. Corti, *Ann. chim. (Rome)* **49,** 2120 (1959).
[i] C. B. Reese, *J. Chem. Soc.* p. 895 (1958).
[j] T. Wieland, C. Fest, and G. Pfleiderer, *Ann. Chem. Liebigs* **642,** 163 (1961).
[k] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.* p. 3318 (1951).
[l] R. M. Acheson, M. L. Burstall, C. W. Jefford, and B. F. Sansom, *J. Chem. Soc.* p. 3742 (1954).
[m] R. J. Light and C. R. Hauser, *J. Org. Chem.* **25,** 538 (1960).
[n] P. Sensi and G. G. Gallo, *Ann. chim. (Rome)* **44,** 232 (1954).

a sharp infrared absorption band near 3600 cm^{-1} which is produced by the free ν O—H. However, if the hydroxyl group is *peri* to a ring nitrogen atom, e.g., as in 8-hydroxyl-1,6-naphthyridine (**29**), a broad band associated with an intramolecularly hydrogen-bonded hydroxyl group occurs at 3470–3395 cm^{-1}. These hydrogen-bonded hydroxyl bands have $\Delta\epsilon_{1/2}$ values of 60–100 cm^{-1} in dilute solution and can be distinguished from the ν NH bands which occur in the same region but have $\Delta\epsilon_{1/2}$ values of 15–30 cm^{-1}. The infrared spectra of α- and γ-hydroxy compounds in the solid state are somewhat less readily interpreted (see, e.g., reference 54) but appear to indicate that these compounds exist in the oxo form in the crystalline state and exhibit N—H···O intermolecular hydrogen bonding.[53]



[29]

The foregoing conclusions are further supported by a refined X-ray analysis of pyrid-2-one, which indicated that the mobile hydrogen atom is attached to the nitrogen atom in the solid state and that individual molecules are bound into helices by N—H···O hydrogen bonds.[55] An oxo structure is also indicated by the molar refractivity of pyrid-2-one.[56] The dipole moment of 4-methoxypyridine is ca. 3.0 debyes in dioxane, whereas the values for pyrid-4-one and its 1-methyl derivative are much higher, ca. 6.0 debyes indicating the

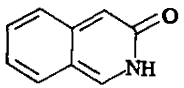
[o] J. A. Gibson, W. Kynaston, and A. S. Lindsey, *J. Chem. Soc.* p. 4340 (1955).
[p] J. Renault, *Bull. soc. chim. France* **20,** 1001 (1953).
[q] S. F. Mason, *J. Chem. Soc.* p. 4874 (1957).
[r] Yu. N. Sheĭnker and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **30,** 79 (1956).
[s] F. Ramirez and A. P. Paul, *J. Org. Chem.* **19,** 183 (1954).
[t] F. Ramirez and A. P. Paul, *J. Am. Chem. Soc.* **77,** 1035 (1955).
[u] F. Ramirez and A. P. Paul, *J. Am. Chem. Soc.* **77,** 3337 (1955).
[v] L. Birkofer and C. Kaiser, *Chem. Ber.* **90,** 2933 (1957).
[w] E. Biekert and L. Enslein, *Chem. Ber.* **93,** 634 (1960).

[54] J. A. Gibson, W. Kynaston, and A. S. Lindsey, *J. Chem. Soc.* p. 4340 (1955).
[55] B. R. Penfold, *Acta Cryst.* **6,** 591 (1953).
[56] K. von Auwers, *Ber. deut. chem. Ges.* **63,** 2111 (1930).

predominance of the oxo form in this solvent.[57,58] The nuclear magnetic resonance spectra of pyrid-4-one and its methylated derivatives indicate that the oxo form also predominates in aqueous solution.[59]

The pK_a method was first used by Tucker and Irvin[44] to determine the proportion of the tautomers of quinol-4-one present at equilibrium and was subsequently applied to many other potentially tautomeric hydroxy compounds[57,60]; these results are summarized in Table I.

3-Hydroxyisoquinolines have been considered to exist as such rather than as **30** on the basis of chemical evidence,[61] and, indeed, the infrared spectrum of this compound was reported to show a νOH band at 2.93μ (3413 cm^{-1}).[62] These results have been questioned, the iso-



[30]

quinol-3-one structure being preferred on the basis of pK_a and of infrared and ultraviolet spectral data.[63]

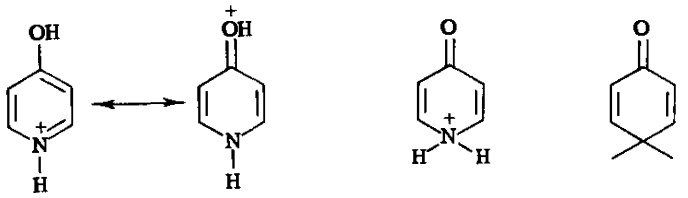
For a discussion of hydroxynaphthyridines, see reference 63a.

C. Pyridone Cations

The theory of mesomerism leads to the prediction that cations of type **31** ↔ **32** should be greatly stabilized relative to those of type **33**, and their predominance has nearly always been assumed. The similarity among the ultraviolet spectra of the cations formed by 4-methoxypyridine, 1-methylpyrid-4-one, and pyrid-4-one was taken to support such assumptions, which are, indeed, implicit in obtaining

[57] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).
[58] D. G. Leis and B. C. Curran, *J. Am. Chem. Soc.* **67**, 79 (1945).
[59] R. A. Y. Jones, A. R. Katritzky, and J. M. Lagowski, *Chem. & Ind. (London)* p. 870 (1960).
[60] S. F. Mason, *J. Chem. Soc.* p. 674 (1960).
[61] W. J. Genslev, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, p. 441. Wiley, New York, 1952.
[62] J. H. Boyer and L. T. Wolford, *J. Org. Chem.* **21**, 1297 (1956).
[63] H. E. Baumgarten, W. F. Murdock, and J. E. Dirks, *J. Org. Chem.* **26**, 803 (1961).
[63a] A. Albert and A. Hampton, *J. Chem. Soc.* p. 505 (1954).

tautomeric constants from pK_a data. Recently, however, Spinner[64]



[31] [32] [33] [34]

pointed out that this spectral evidence is not compelling in the case of pyrid-4-one since the ultraviolet spectra of cyclohexadienones of type **34** are also similar to those of the pyrid-4-one cations, and both the infrared and Raman spectra of these cations have been interpreted to favor structures of type **33**.[64,65] Nuclear magnetic resonance data, on the other hand, strongly support structures of type **31** ↔ **32**.[59,66] The cations of acyclic amides are also formed by proton addition to oxygen.[67]

D. β-Hydroxypyridines

Many of the properties of β-hydroxypyridines are typical of phenols. It was long assumed that they existed exclusively in the hydroxy form, and early physical measurements seemed to confirm this. For example, the ultraviolet spectrum of a methanolic solution of 3-hydroxypyridine is very similar to that of the 3-methoxy analog,[41] and the value of the dipole moment of 3-hydroxypyridine obtained in dioxane indicates little, if any, zwitterion formation.[57] However, it has now become clear that the hydroxy form is greatly predominant only in solvents of low dielectric constant. Comparison of the pK values of 3-hydroxypyridine with those of the alternative methylated forms indicated that the two tautomeric forms are of comparable stability in aqueous solution[60] (Table II), and this was confirmed using ultraviolet spectroscopy.[68] The ratios calculated from the ultraviolet spectral data are in good agreement with those de-

[64] E. Spinner, *J. Chem. Soc.* p. 1226 (1960).
[65] P. Sensi and G. G. Gallo, *Ann. chim. (Rome)* **44**, 232 (1954).
[66] A. R. Katritzky and R. A. Y. Jones, *Proc. Chem. Soc.* p. 313 (1960).
[67] A. R. Katritzky and R. A. Y. Jones, *Chem. & Ind. (London)* p. 722 (1961).
[68] S. F. Mason, *J. Chem. Soc.* p. 5010 (1957).

TABLE II
RATIO OF THE ZWITTERION FORM TO THE HYDROXY FORM (pK_T) FOR β-HYDROXYPYRIDINES

Compound	pK Method[a]	UV Method[b]	IR Method[c]
3-Hydroxypyridine[d]	−0.08	0.10	pr OH[i]
	+0.07[f]		
	0.08[g]		
3-Hydroxyquinoline	−1.08	−1.19	pr OH
4-Hydroxyisoquinoline[e]	0.46	0.58	pr OH
8-Hydroxy-1,6-naphthyridine	0.09	−0.05	pr OH
Pyridoxine (**38**)	0.90[g]	—	—
Pyridoxal (**40, 41**)	1.08[g]	—	—
Pyridoxamine	1.60[g]	—	—
2-Hydroxymethyl-3-hydroxypyridine	—	0.26[h]	—
4-Hydroxymethyl-3-hydroxypyridine	—	0.23[h]	—
3-Hydroxypyridine-2-aldehyde	—	0.11[i]	—
3-Hydroxypyridine-4-aldehyde	—	−0.22[i]	—

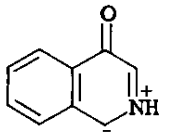
[a] S. F. Mason, *J. Chem. Soc.* p. 674 (1958), where not otherwise indicated.
[b] S. F. Mason, *J. Chem. Soc.* p. 5010 (1957), where not otherwise indicated.
[c] S. F. Mason, *J. Chem. Soc.* p. 4874 (1957).
[d] A value of −0.12 was obtained using the Hammett equation [H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4445 (1955)].
[e] Using the Hammett equation, $pK_T = 0.12$ [A. Bryson, *J. Am. Chem. Soc.* **82**, 4871 (1960)].
[f] D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc* **77**, 2431 (1955).
[g] Value obtained by UV extrapolation [D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.* **77**, 2431 (1955)].
[h] K. Nakamoto and A. E. Martell, *J. Am. Chem. Soc.* **81**, 5857 (1959).
[i] K. Nakamoto and A. E. Martell, *J. Am. Chem. Soc.* **81**, 5863 (1959).
[j] This notation means that the hydroxy form is predominant in the equilibrium mixture.

termined from pK_a values (Table II) and with the pK_T values of −0.12[69] and −0.10[70] obtained for 3-hydroxypyridine using the Hammett equation.

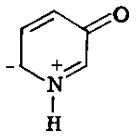
The changes found in the ratio of the zwitterion to the hydroxy form for β-hydroxypyridines with fused benzene rings have been discussed by Mason.[68] The proportion of the zwitterion form decreases

[69] H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4445 (1955).
[70] A. Bryson, *J. Am. Chem. Soc.* **82**, 4871 (1960).

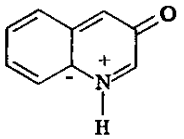
in the order 4-hydroxyisoquinoline, 3-hydroxypyridine, and 3-hydroxyquinoline; therefore, the stabilization effected by structures **35**, **36**, and **37** should become successively smaller. Later work based on the Hammett equation is in general agreement with these considerations.[70]



[35]

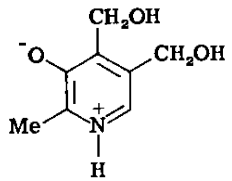


[36]

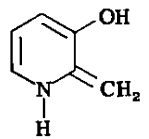


[37]

The ultraviolet spectrum of vitamin B_6, or pyridoxine, measured in aqueous ethanol varies with the composition of the solvent indicating that this compound is in equilibrium with the zwitterion form **38**.[71] The equilibrium constant in pure water was obtained by extrapolation.[72] Prior to this, equilibria which involved tautomers of type **39** had been suggested for vitamin B_6,[73] but see Section VI,A. In the case of pyridoxal, an additional equilibrium, **40** ⇌ **41**, occurs (cf. Section VIII); other pyridoxal analogs have also been studied[74,75] (Table II).

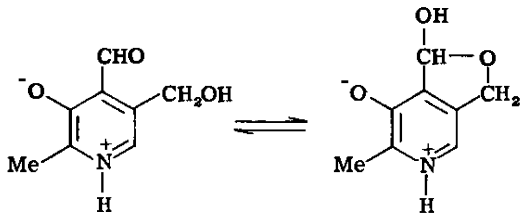


[38]



[39]

[71] S. A. Harris, T. J. Webb, and K. Folkers, *J. Am. Chem. Soc.* **62**, 3198 (1940).
[72] D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.* **77**, 2431 (1955).
[73] A. Itiba and K. Miti, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **36**, 1 (1939).
[74] R. P. Welcher, D. W. Kaiser, and V. P. Wystrach, *J. Am. Chem. Soc.* **81**, 5663 (1959).
[75] K. Nakamoto and A. E. Martell, *J. Am. Chem. Soc.* **81**, 5857 (1959).

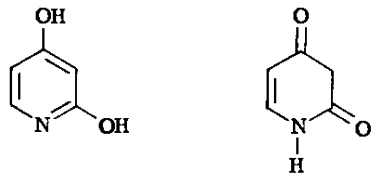


[40] [41]

As mentioned in Section II,B, solutions of β-hydroxypyridines in the nonpolar solvents chloroform and carbon tetrachloride show sharp infrared absorption bands near 3600 cm^{-1} indicating that they exist in the hydroxy form. Infrared spectral data also led Mason[53] to conclude that β-hydroxypyridines probably exist largely as such in the solid state and exhibit O—H···O hydrogen bonding, a conclusion which is contrary to an earlier proposal[65] favoring a zwitterion structure.

E. Hydroxypyridones

α,α- or α,γ-Dihydroxypyridines, e.g., **42**, can also tautomerize to *o*- (**12**, Z = NH) or *p*-quinonoid forms (**13**, Z = NH) or to the nonaromatic form **43**. After inconclusive early work,[76] ultraviolet spectral comparisons with all the methylated forms indicated that 2,4-dihydroxypyridine exists predominantly in the 4-hydroxy-2-oxo form (**12**, Z = NH),[77] and an analogous structure has been assigned to the 3-bromo derivative.[78] Infrared spectra also support the 4-hydroxy-2-



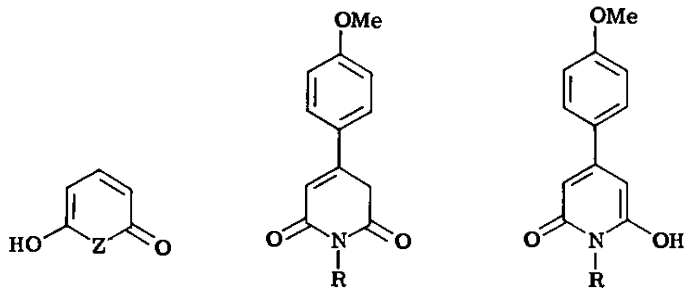
[42] [43]

oxo structure for 2,4-dihydroxy-6-methylpyridine which served as a

[76] H. M. Woodburn and M. Hellmann, *Rec. trav. chim.* **70**, 813 (1951).
[77] H. J. den Hertog and D. J. Buurman, *Rec. trav. chim.* **75**, 257 (1956).
[78] C. R. Kolder and H. J. den Hertog, *Rec. trav. chim.* **79**, 474 (1960).

model compound for discussion of the tautomerism of the complex natural product azadesmethylisoaureothin.[79]

It seems probable that glutaconimides exist predominantly as **44** (Z = NH), although there is little direct evidence for this formulation (cf. reference 80) other than some tentative infrared data[81] which



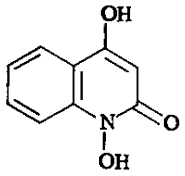
[44] [45] [46]

were apparently interpreted to indicate that the tautomeric compound **45** ⇌ **46** exists as **45** in Nujol and as a mixture of **45** and **46** in chloroform solution. The predominant form of *N*-hydroxyglutaconimides has been suggested to be **44** (Z = NOH) on the basis of physical data.[82]

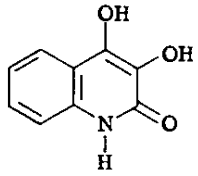
On the basis of its reaction with diazomethane, 2,4-dihydroxyquinoline was reported to exist as 4-hydroxyquinol-2-one in the solid state and as an equilibrium mixture of this form with 2-hydroxyquinol-4-one in solution.[83,84] Using the infrared criteria for *o*- and *p*-quinonoid forms (see Section II,L), the spectra of 2,4-dihydroxy-pyridine and -quinoline indicated that both quinonoid forms, e.g., **12** (Z = NH) and **13** (Z = NH), were present and that the nonaromatic form (**43**) was absent.[53]

[79] K. Yamada, H. Nakata, and Y. Hirata, *Bull. Chem. Soc. Japan* **33**, 1298 (1960).
[80] C. E. Dalgliesh, A. W. Johnson, and C. Buchanan, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IB, p. 1003. Elsevier, Amsterdam, 1952.
[81] D. E. Ames and T. F. Grey, *J. Chem. Soc.* p. 2310 (1959).
[82] D. E. Ames and T. F. Grey, *J. Chem. Soc.* p. 631 (1955).
[83] M. Vardar, *Rev. fac. sci. univ. Istanbul* **16A**, 243 (1951).
[84] F. Arndt, L. Ergener, and O. Kutlu, *Chem. Ber.* **86**, 951 (1953).

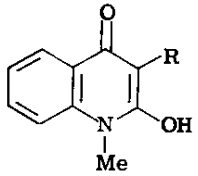
The isolation of two tautomers of 2,3,4-trihydroxyquinoline has been reported,[85] but one was later identified as the isomeric 1,2,4-trihydroxy compound **47**.[86] The fact that 2,3,4-trihydroxyquinoline is oxidized more slowly than its *N*-methyl derivative was considered to show that it existed in an oxo form.[87] The product resulting from



[47]



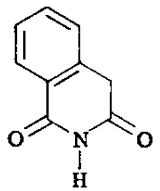
[48]



[49]

treatment of 2,3,4-trihydroxyquinoline with diazomethane led Vardar[83] to conclude that it exists mainly as **48**, whereas its *N*-methyl derivative (**49**, R = OH) and the corresponding compounds **49** (R = H) and **49** (R = OMe) yielded largely the 2-methoxy compounds with this reagent. It would appear that this series of compounds could profitably be reinvestigated.

In the isoquinoline series, infrared spectral data favor nonaromatic forms of type **50** for homophthalimide,[53] a series of substituted homophthalimides,[88] and certain *N*-hydroxyhomophthalimides[89]; the predominance of this structure type gains support from the ultraviolet spectra of homophthalimide and *N*-ethylhomophthalimide.[90]

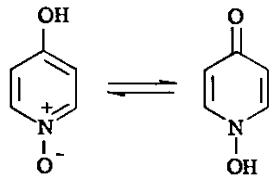


[50]

[85] G. Heller and W. Tischner, *Ber. deut. chem. Ges.* **42**, 4555 (1909).
[86] F. Arndt, L. Ergener, and O. Kutlu, *Chem. Ber.* **86**, 957 (1953).
[87] L. Loewe, M. Vardar, E. Ayça, *Rev. fac. sci. univ. Istanbul* **16A**, 241 (1951).
[88] A. L. Bluhm, *Spectrochim. Acta* **13**, 93 (1958).
[89] D. E. Ames and T. F. Grey, *J. Chem. Soc.* p. 3518 (1955).
[90] W. Marckwald and E. Meyer, *Ber. deut. chem. Ges.* **33**, 1885 (1900).

F. Hydroxypyridine 1-Oxides (1-Hydroxypyridones)

The pK_a values of 4-hydroxypyridine 1-oxide (**51** ⇌ **52**) and the methylated derivatives of both tautomeric forms indicate that the parent compound exists as a mixture containing comparable amounts of both forms in aqueous solution.[91] Nuclear magnetic resonance spectra support this conclusion,[59] but the ultraviolet spectra of the tautomeric compound and both alkylated derivatives are too similar to give information concerning the structural nature of the former.[91,92]



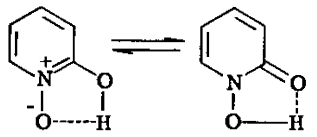
[51] [52]

4-Hydroxypyridine 1-oxide is insoluble in chloroform and other suitable solvents, and, although the solid-state infrared spectrum indicates that strong intermolecular hydrogen bonding occurs,[93] no additional structural conclusions could be reached.[51] Jaffé has attempted to deduce the structure of 4-hydroxypyridine 1-oxide using the Hammett equation[69,94,95] and molecular orbital calculations.[96] This tautomeric compound reacts with diazomethane to give both the 1- and 4-methoxy derivatives,[97] and the relation of its structure to other chemical reactions has been discussed by Hayashi.[98]

Fixed derivatives of the two tautomeric forms of 2-hydroxypyridine 1-oxide do not give cations of similar structure[91] which precludes the use of pK_a measurements to elucidate its structure (cf. preceding

[91] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* p. 4375 (1957).
[92] E. Shaw, *J. Am. Chem. Soc.* **71**, 67 (1949).
[93] G. Costa, P. Blasina, and G. Sartori, *Z. physik. Chem. (Frankfurt)* **7**, 123 (1956).
[94] H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.* **77**, 4441 (1955).
[95] H. H. Jaffé, *J. Org. Chem.* **23**, 1790 (1958).
[96] H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4448 (1955).
[97] E. Ochiai and E. Hayashi, *J. Pharm. Soc. Japan* **67**, 151 (1947); *Chem. Abstr.* **45**, 9540 (1951).
[98] E. Hayashi, *J. Pharm. Soc. Japan* **71**, 213 (1951); *Chem. Abstr.* **46**, 4541 (1952).

article I, Section III,A). The 1-hydroxypyrid-2-one formulation (**54**) was suggested by ultraviolet spectral comparisons with pyrid-2-one[99] and with the alternative alkylated isomers,[92] but this evidence is not as conclusive as it was first thought to be.[91] Evidence for strong intramolecular hydrogen bonding in **53** or **54** and an indication that structure **54** represents the most important tautomeric form is provided by the infrared spectrum[51,91]; some substituted 1-hydroxypyrid-2-ones are discussed with respect to their infrared spectra in references 100 and 101.

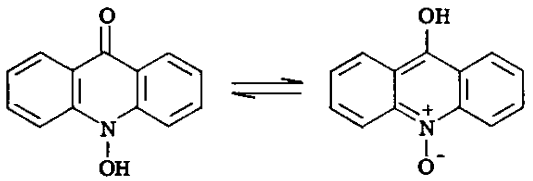


[53] [54]

The infrared spectra of 2- and 4-hydroxyquinoline 1-oxide have been interpreted to favor forms **55** and **56**, respectively.[102] Lehmstedt[103] has discussed the tautomerism of 10-hydroxyacridone (**57** $\rightleftharpoons$ **58**) but reached no definite conclusions. Igeta[104] investigated the

[55] [56]

[99] K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *J. Chem. Soc.* p. 2091 (1949).
[100] R. Adams and S. Miyano, *J. Am. Chem. Soc.* **76**, 3168 (1954).
[101] R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.* **78**, 2393 (1956).
[102] C. Kaneko, *Yakugaku Zasshi* **79**, 428 (1959).
[103] K. Lehmstedt, *Ber. deut. chem. Ges.* **68**, 1455 (1935).
[104] H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **7**, 938 (1959).

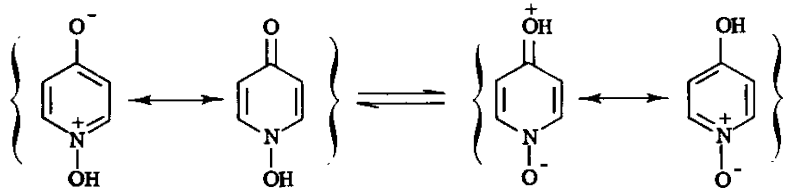


[57] [58]

[59] [60]

tautomerism of 3-hydroxypyridazine 1-oxide and tentatively concluded that it exists as **59**; however, the present authors do not feel that structure **60** has been excluded by this study.

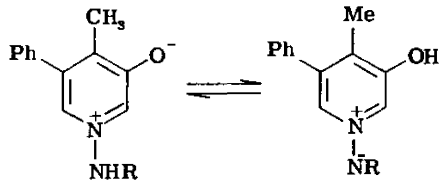
Consideration of the various possibilities for mesomerism leads to an explanation of the tautomeric differences between hydroxypyridine 1-oxides and the corresponding pyridones. For example, structures of type **61** exert a smaller stabilizing effect on 1-hydroxypyrid-4-one (**62**) than the corresponding structures do on pyrid-4-one, and, conversely, structures of type **63** exert a greater stabilizing effect on 4-hydroxypyridine 1-oxide (**64**) than the corresponding structures do on 4-hydroxypyridine. Consequently, the positions of the tautomeric equilibria are such that a greater proportion of the C—OH form is present for pyridine 1-oxides than for the corresponding pyridines.[91]



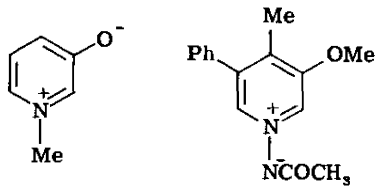
[61] [62] [63] [64]

G. Hydroxypyridine 1-Imides[105]

The predominance of structure **65** (R = H) in the equilibrium **65** ⇌ **66** has been reported on the basis of the ultraviolet spectral similarity of the potentially tautomeric compound and of **67**. However, when R = $COCH_3$, this hydroxypyridine 1-imide reacts with diazomethane to yield **68**, which has been interpreted to indicate that **66** is the predominant tautomer; this conclusion is supported by the resultant changes in the pK_a values when the acetyl group is replaced by other acyl groups.



[65] [66]

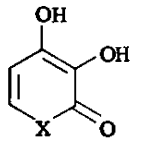


[67] [68]

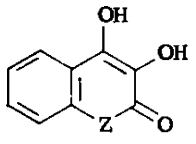
H. Reductones (Dihydroxy-pyridones and -pyranones)

Compounds of types **69** and **70** are classified as reductones. Non-aromatic reductones, such as **71** and **72**, exist entirely in the lactam or lactone form, but an appreciable proportion of aromatic reductones is in the γ-oxo form (cf. **73**) at equilibrium.[106] These conclusions are largely based on studies of 3,4-dihydroxythiacoumarin[107-108a] and 3,4-dihydroxycoumarin[7] (**70**, Z = S and O, respectively). Dihydroxypyrones,[109(a)] coumarin- and chromone-diols,[109(b)] thiacoumarin- and thiachromone-diols,[109(c)] pyridonediols,[109(d)] and quinolonediols[109(e)] have been reviewed.

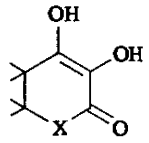
[105] J. A. Moore and J. Binkert, *J. Am. Chem. Soc.* **81**, 6045 (1959).
[106] H. Dahn and H. Hauth, *Helv. Chim. Acta* **40**, 2249 (1957).
[107] F. Arndt, L. Loewe, and E. Ayça, *Chem. Ber.* **84**, 329 (1951).
[108] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **62**, 36 (1929).
[108a] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **68**, 1572 (1935).



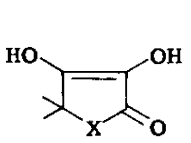
[69]



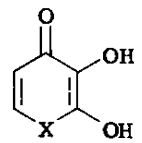
[70]



[71]



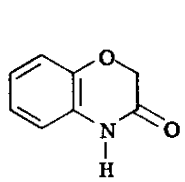
[72]



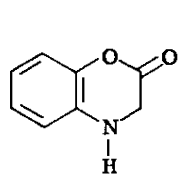
[73]

I. Oxazinones

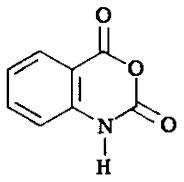
Structures **74–76** represent the predominant tautomeric forms of each of the hydroxyazines indicated in chloroform and in the solid state since both C=O and NH absorption bands occur in their infrared spectra, but OH bands are absent.[110]



[74]



[75]



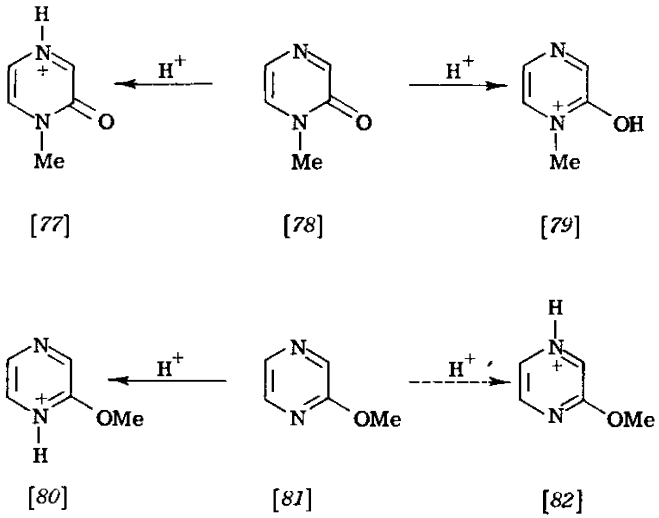
[76]

J. Hydroxyazines (General Discussion)

If a six-membered ring contains two or more nitrogen atoms, the

[109] H. von Euler and B. Eistert, "Chemie und Biochemie der Reduktone und Reduktonate." (a) p. 164, (b) p. 168, (c) p. 172, (d) p. 176, (e) p. 181, (f) p. 185. F. Enke, Stuttgart, Germany, 1957.
[110] D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.* p. 2916 (1957).

number of possible tautomeric forms increases, and it becomes much more difficult to determine the relative importance of the various forms. Determination of the proportion of the various tautomers present at equilibrium by the pK_a method is not always possible because common cations are not always formed. This can be illustrated by 2-hydroxypyrazine, where, to apply the pK_a method, it must be assumed that 1-methylpyrazin-2-one and 2-methoxypyrazine form a common cation (i.e., **78** gives **79**, and **81** gives **80**) and that the ionic species **77** and **82** are unimportant. The validity of such assumptions can, of course, often be determined from the ultraviolet spectra of the compounds, and in this particular case Cheeseman[111] has shown that



common cations are not formed. Common cations are also not formed by compounds containing two hetero nitrogen atoms *beta* to each other (see following). In general, however, both the ultraviolet and the infrared spectral methods are applicable to the investigation of tautomerism in the hydroxyazines.

K. Pyridazinones, Cinnolinones, and Phthalazinones

Both pK and ultraviolet spectral data indicate that 3- and 4-monohydroxy-pyridazines and -cinnolines exit predominantly in the oxo

[111] G. W. H. Cheeseman, *J. Chem. Soc.* p. 242 (1960).

form (Table III). The infrared spectra of both pyridazin-3-one and its 6-methyl derivative contain a ν N—H band, substantiating the oxo formulation[53,112,113]; similar evidence has been reported in support of oxo structures for the 4- and 5-carboxy-6-chloro derivatives of pyridazin-3-one[114] and for pyridazin-4-one.[53] The fact that 3-hydroxycinnoline is a weaker acid than 3-hydroxyquinoline is in agreement with its formulation as cinnolin-3-one, since if it existed in the hydroxy form it should be a stronger acid than 3-hydroxyquinoline.[115] The cinnolin-3-one formulation has been further confirmed by Mason[53] using infrared spectroscopy.

There is a discrepancy in the literature concerning 4-hydroxycinnoline. Whereas two measurements of pK_a values indicate that the cinnolinone structure predominates by a large factor in aqueous solution (see Table III), comparison of the ultraviolet spectra of 4-hydroxycinnoline and both methylated forms measured in ethanolic solution was considered to show that cinnolin-4-one (**83**) and its 3-,

TABLE III

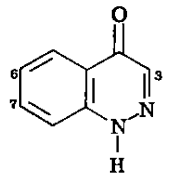
Ratio of the Oxo Form to the Hydroxy Form (pK_T) for 3- and 4-Monohydroxy-pyridazines and -cinnolines

Compound	pK Method	UV Method
3-Hydroxypyridazine	4.3[a]	pr[e,f,g,h]
3-Hydroxy-6-methylpyridazine	—	pr[g]
6-Aryl-3-hydroxypyridazines (various)	—	pr[i]
4-Hydroxypyridazine	2.6[a]	pr[f]
3-Hydroxycinnoline (and derivatives)	pr[b]	probably pr[i]
4-Hydroxycinnoline	3.6[c,d]	See text

[a] S. F. Mason, *J. Chem. Soc.* p. 674 (1958).
[b] H. E. Baumgarten, W. F. Murdock, and J. E. Dirks, *J. Org. Chem.* **26,** 803 (1961).
[c] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).
[d] A. R. Osborn and K. Schofield, *J. Chem. Soc.* p. 4207 (1956).
[e] The notation "pr" indicates that the oxo form predominates in the equilibrium mixture.
[f] S. F. Mason, *J. Chem. Soc.* p. 5010 (1957).
[g] W. G. Overend, L. M. Turton, and L. F. Wiggins, *J. Chem. Soc.* p. 3500 (1950).
[h] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **37,** 1298 (1954).
[i] E. A. Steck and F. C. Nachod, *J. Am. Chem. Soc.* **79,** 4408 (1957).
[j] E. J. Alford and K. Schofield, *J. Chem. Soc.* p. 1811 (1953).

[112] Yu. N. Sheĭnker and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **30,** 79 (1956).
[113] W. G. Overend, L. M. Turton, L. F. Wiggins, *J. Chem. Soc.* p. 3500 (1950).
[114] T. Kuraishi, *Chem. Pharm. Bull. (Tokyo)* **6,** 551 (1958).
[115] E. J. Alford and K. Schofield, *J. Chem. Soc.* p. 1811 (1953).

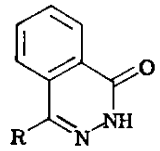
6-, and 7-methyl derivatives exist in equilibrium with ca. 30% of the



[83]

corresponding hydroxy forms.[45] Changing from water to ethanol as a solvent would not be expected to cause a change of this magnitude, especially since the infrared spectra of these compounds indicate that the 4-one structure predominates both in the solid state and in chloroform solution.[53] Cinnolin-4-one structures have been proposed to represent the predominant forms of the 3-carboxylic acid and the 6-nitro compound on the basis of their ultraviolet spectra.[45]

Although early investigators[116] considered that 4-hydroxy-1-methylphthalazine existed as such in neutral solution, they refer to basicity data which, in the light of present knowledge, would lead to assignment of the 1-methylphthalazin-4-one structure (**84**, R = Me) to the predominant tautomer. The correctness of the oxo structure for phthalazin-1-one (**84**, R = H) has been demonstrated using infrared spectroscopy.[53,112]

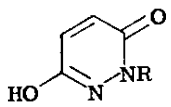


[84]

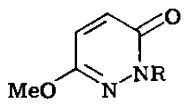
The structure of maleic hydrazide has been extensively investigated. In 1954, a Swiss group[117] assigned the 6-hydroxypyridazin-3-one (**85**, R = H) structure to maleic hydrazide on the basis of its

[116] F. M. Rowe and A. T. Peters, *J. Chem. Soc.* p. 1331 (1933).
[117] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **37**, 1298 (1954).

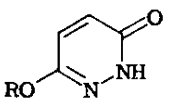
ultraviolet spectrum, and this assignment was supported by Miller and White's comparison of its ultraviolet spectrum and pK value with those of the four different methylated derivatives.[118] Investigation of the infrared spectra and pK data of maleic hydrazide and its methyl derivatives led Sheĭnker and his collaborators[112,119,120] to the same conclusions. The infrared spectrum of maleic hydrazide shows both ν OH and ν C=O bands, and maleic hydrazide and its mono-*N*-methyl derivative are acids of appreciable strength, whereas the mono-*O*-methyl derivative is not acidic. The Russian investigators also reported that the ultraviolet spectra of these compounds were too similar to permit definite conclusions concerning the structure of maleic hydrazide. Earlier, the relative stabilities of the various methyl derivatives had been discussed with respect to the tautomerism of maleic hydrazide.[121] Diazomethane has been reported to convert the



[85]



[86]



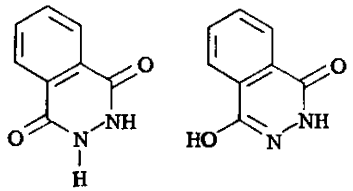
[87]

parent compound rapidly into **86** (R = H) followed by slow conversion into **86** (R = Me), and these results were correctly interpreted as supporting the monooxo–monohydroxy structure.[122] Feuer and Rubinstein[123] have presented basicity data to support structures **85** and **87** for the mono-*N*- and -*O*-acetylated and -sulfonylated derivatives. A recent report that the nuclear magnetic resonance spectrum of maleic hydrazide measured in dimethyl sulfoxide is in accord with a dioxo formulation[124] is probably the result of incorrect interpretation of the data because of rapid proton exchange in this

[118] D. M. Miller and R. W. White, *Can. J. Chem.* **34**, 1510 (1956).
[119] Yu. N. Sheĭnker, T. V. Gortinskaya, T. P. Sycheva, *J. chim. phys.* **55**, 217 (1958).
[120] Yu. N. Sheĭnker, T. V. Gortinskya, and T. P. Sycheva, *Zhur. Fiz. Khim.* **31**, 599 (1957).
[121] K. Eichenberger, A. Staehelin, and J. Druey, *Helv. Chim. Acta* **37**, 837 (1954).
[122] H. Hellmann and I. Löschmann, *Chem. Ber.* **89**, 594 (1956).
[123] H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.* **80**, 5873 (1958).
[124] R. Gompper and P. Altreuther, *Z. anal. Chem.* **170**, 205 (1959).

solvent between oxygen and nitrogen atoms of the heterocyclic compound.

Phthalic hydrazide has received even more attention than maleic hydrazide, the potential tautomerism having been discussed since 1925.[125] Chemical evidence has been advanced both for the dioxo form **88**[125,126] and for the dihydroxy form **89**,[116] and it has been further suggested that a change of tautomeric forms occurs just below the melting point.[126] The Russian investigation of maleic hydrazide[112,119,120] also included phthalic hydrazide and demonstrated that the latter compound should be assigned the 4-hydroxyphthalazin-1-one structure (**89**). Although an early ultraviolet spectral study yielded no conclusive structural information,[127] Elvidge and Redman concluded recently that the ultraviolet spectra of 1-hydroxyphthalazin-4-one and its derivatives provide the most reliable evidence for structure **89** and confirmed this conclusion using infrared spectroscopy.[128]



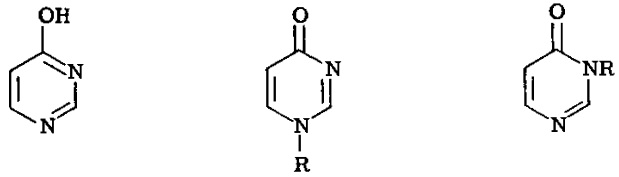
[*88*] [*89*]

L. Pyrimidinones and Quinazolinones

Pyrimidinones have been extensively investigated because of their importance in the chemistry of natural products. Initially, the infrared spectra of the hydroxypyrimidines were interpreted to favor their existence in the hydroxy form[129]; however, in 1952 Short and Thompson[130] reinvestigated these compounds and concluded that pyrimidin-2- and -4-one probably exist in the oxo form. Solid-state infrared spectra were used in this early work which probably accounts for the difficulties encountered in their interpretation. Brown and his associates[131,132] later reported that the infrared spectra of pyrimidin-2- and -4-one and their *N*-methyl derivatives showed a ν C=O absorption band in the 1700–1600 cm^{-1} region which was absent from the spectra of the corresponding methoxy compounds.

[125] D. Radulescu and V. Georgescu, *Bull. soc. chim. France* **37**, 881 (1925).
[126] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.* p. 16 (1937).
[127] D. Biquard and P. Grammaticakis, *Bull. soc. chim. France* **9**, 675 (1942).
[128] J. A. Elvidge and A. P. Redman, *J. Chem. Soc.* p. 1710 (1960).
[129] I. A. Brownlie, *J. Chem. Soc.* p. 3062 (1950).
[130] L. N. Short and H. W. Thompson, *J. Chem. Soc.* p. 168 (1952).

4-Hydroxypyrimidine (**89a**) can tautomerize to two alternative oxo forms, **90** (R = H) and **91** (R = H). The infrared solution spectra of pyrimidin-2- and -4-one clearly indicate the presence of both C=O and NH groups,[53] and by using these spectra Mason demonstrated that pyrimidin-4-one existed predominantly in the *o*-quinonoid



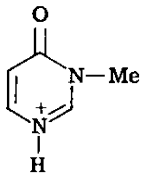
[*89a*] [*90*] [*91*]

form. For monoaza compounds, fixed *o*-quinonoid type structures cause absorption at 3420–3360 cm^{-1} and the fixed *p*-quinonoid types at 3445–3415 cm^{-1}; it was shown by analogy that the *o*-quinonoid forms of tautomeric diaza compounds predominate, e.g., **91** (R = H). The differences between the ultraviolet spectra of *o*- and *p*-quinonoid forms of heterocyclic compounds have been discussed.[133]

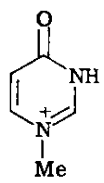
Between 1951 and 1953 investigations by three English groups[131,132,134,135] clearly demonstrated the preponderance of the oxo forms of pyrimidin-2- and -4-ones by comparing the ultraviolet spectra of these compounds with those of the *N*- and *O*-alkylated derivatives. The *o*-quinonoid form **91** (R = H) is favored by the evidence that *N*-methylation of the 6-methyl derivative of **89a** does not cause a bathochromic shift in the ultraviolet spectrum (*N*-methylation of pyrid-4-one causes a bathochromic shift, but this is not observed for pyrid-2-one).[134] The isomeric *N*-methyl derivatives of pyrimidin-4-ones [e.g., **91** (R = Me) and **90** (R = Me)] form similar cations (e.g., **92** and **93**), and hence the equilibrium constant between

[131] D. J. Brown and L. N. Short, *J. Chem. Soc.* p. 331 (1953).
[132] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.* p. 211 (1955).
[133] J. A. Berson, *J. Am. Chem. Soc.* **75**, 3521 (1953).
[134] J. R. Marshall and J. Walker, *J. Chem. Soc.* p. 1004 (1951).
[135] M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.* p. 3716 (1952).

90 (R = H) and **91** (R = H) can be calculated by the pK method[60]; for pyrimidin-4-one log K_{op}[136] is 0.18. In reasonable agreement with



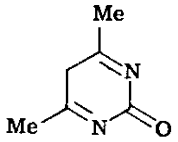
[92]



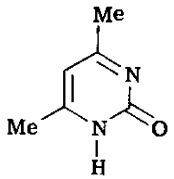
[93]

this value, log K_{op} for pyrimidin-4-one was found to be 0.40 from ultraviolet spectral data, whereas a value of 0.85 was determined for quinazolin-4-one.[68] The predominance of the oxo form of 6-aminopyrimidin-4-one has been shown using ultraviolet spectroscopy,[137] and this formulation is supported by pK_a data.[138]

An X-ray crystallographic study of 2-hydroxy-4,6-dimethylpyrimidine led to no conclusions regarding its structure.[139] Because of the rapid exchange of the NH protons of pyrimidin-2-one both in dimethyl sulfoxide and in water, nuclear magnetic resonance spectroscopy does not afford positive evidence for either the oxo or the hydroxy formulation.[140] The statement that 4,6-dimethylpyrimidin-2-one had been isolated in two modifications, **94** and **95**,[141] was soon disproved.[142]



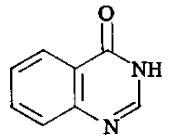
[94]



[95]

[136] K_{op} is the ratio of *ortho* (cf. **91**, R = H) to *para* form (cf. **90**, R = H).
[137] W. Pfleiderer and E. Liedek, *Ann. Chem. Liebigs* **612**, 163 (1958).
[138] D. J. Brown and J. S. Harper, *J. Chem. Soc.* p. 1298 (1961).
[139] G. J. Pitt, *Acta Cryst.* **1**, 168 (1948).
[140] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **16**, 459 (1960).
[141] M. T. deHaan, *Rec. trav. chim.* **27**, 162 (1908).
[142] F. M. Jaeger, *Z. Kryst. Mineral.* **44**, 561 (1908).

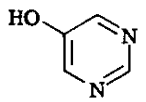
Quinazolin-4-one and its 6-nitro derivative were both shown to exist predominantly in the *o*-quinonoid form (cf. **96**) by ultraviolet spectral comparisons of the parent compound with the *O*-methyl derivative and with the two *N*-methyl analogs.[45] The existence of quinazolin-2- and -4-ones in an oxo-type structure was demonstrated in 1952[143] by using solid-state infrared data and later confirmed by



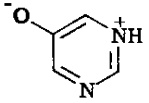
[96]

using solution spectra[53]; evidence based on solution infrared spectra also showed that quinazolin-4-one exists in the *o*-quinonoid form.[53]

5-Hydroxypyrimidine (**97**), which cannot exist in an uncharged pyrimidinone form, and its derivatives are phenolic in character,[144]



[97]



[98]

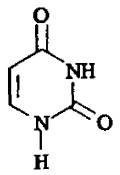
but ultraviolet spectral data indicate that at least 2% of the zwitterion form (**98**) is present at equilibrium.[68]

M. Uracil, Cytosine, and Related Compounds

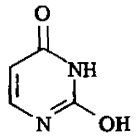
These compounds have been extensively investigated because they are important nucleic acid constituents. Uracil has been shown conclusively to exist predominantly as pyrimidine-2,4-dione (**99**) both by a refined X-ray crystallographic technique in which the positions

[143] H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.* **74**, 4834 (1952).
[144] J. H. Chesterfield, J. F. W. McOmie, M. S. Tute, *J. Chem. Soc.* p. 4590 (1960).

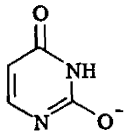
of the hydrogen atoms were determined directly[145] (cf. reference 146) and by an ultraviolet spectral comparison with the various alkylated forms.[134,147,148] Austin's assignment[149] of structure **100** to uracil in



[99]



[100]



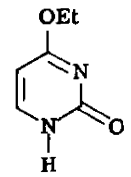
[101]

1934 on the basis of ultraviolet spectral data has been disproved. Early infrared data substantiated the presence of at least one oxo group in uracil,[130] and later spectral data established dioxo formulations for 1- and 3-methyluracil[53] and uracil itself.[150] Ultraviolet studies indicate that the monoanion of uracil is **101**.[147] 5-Nitrouracil has been shown to exist predominately in the dioxo form by using ultraviolet spectroscopy.[151]

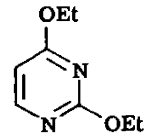
Shugar and Fox[147] reported that 4-ethoxypyrimidin-2-one exists in the oxo form **102** since its ultraviolet spectrum is different from that of **103**. They further claimed that the isomeric compound, 2-ethoxy-4-hydroxypyrimidine, existed in the hydroxy form (**104**); however, reexamination of the ultraviolet spectral data suggests that this unlikely conclusion may be incorrect, and the infrared spectrum of **104** does, indeed, show a carbonyl absorption band.[152] 2-Methylthiopyrimidin-4-one has been reported to exist in the hydroxy form,[147] but this to appears unlikely.

For the equilibrium **105** $\rightleftharpoons$ **106**, Katritzky and Waring[152] have reported pK_T values of 3.3 (or 4.0) and 1.7 (or 3.3), in favor of the dioxo form, when R is H and Br, respectively, and have discussed

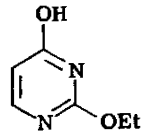
[145] G. S. Parry, *Acta Cryst.* **7**, 313 (1954).
[146] K. Hoogsteen, *Acta Cryst.* **13**, 1050 (1960).
[147] D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta* **9**, 199 (1952).
[148] J. R. Loofbourow, M. M. Stimson, and M. J. Hart, *J. Am. Chem. Soc.* **65**, 148 (1943).
[149] J. E. Austin, *J. Am. Chem. Soc.* **56**, 2141 (1934).
[150] C. L. Angell, *J. Chem. Soc.* p. 504 (1961).
[151] D. J. Brown, *J. Chem. Soc.* p. 3647 (1959).
[152] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.* p. 1541 (1962).



[102]

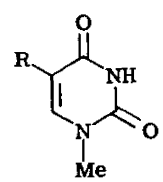


[103]

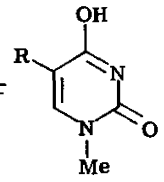


[104]

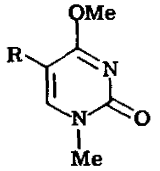
these results with respect to the mutagenesis theory. These pK_T values were obtained using the basicity method, after establishing by ultraviolet spectroscopy that compounds of types **105** and **107** formed cations of similar structure. Unfortunately the exact values of K_T are in doubt because these compounds are not Hammett bases.[152]



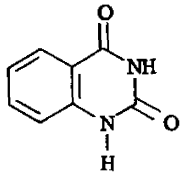
[105]



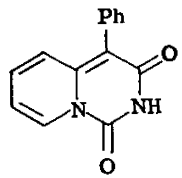
[106]



[107]



[108]



[108a]

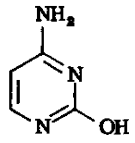
Quinazoline-2,4-dione (**108**) has been assigned the dioxo formulation on the basis of its infrared spectrum.[143] A dioxo structure has also been demonstrated for the derivative **108a** by ultraviolet spectral comparisons and infrared data.[152a]

Although cytosine was assigned structure **109** on the basis of early infrared spectral studies,[153] and other infrared and ultraviolet spectral

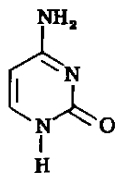
[152a] A. Hunger and K. Hoffmann, *Helv. Chim. Acta* **40**, 1319 (1957).
[153] E. K. Blout and M. Fields, *J. Am. Chem. Soc.* **72**, 479 (1950).

data were also interpreted in favor of an "enol" formulation,[154] the oxo-amino structure **110** seems much more probable and is, indeed, supported by ultraviolet[147] and by later infrared spectral evidence (see reference 150 and references therein). Recently, proton resonance spectra were interpreted in favor of structures **110a** and **110b** for cytosine and its cation,[154a] but it has now been shown that fast proton exchange occurs in these species and cannot be neglected.[154b,154c] By using the basicity method, the value of pK_T for the equilibrium **110** $\rightleftharpoons$ **110c** has been shown to be 3.0 in favor of **110**.[154c] For a discussion of the tautomerism of the amino group of cytosine, see Section IV,D. It has been suggested that cytosine tautomerizes to **111** on ultraviolet irradiation,[155] but no convincing evidence is offered for this *a priori* unlikely behavior. Isocytosine has been assigned an oxo-amino structure on the basis of infrared and ultraviolet spectroscopic studies.[154]

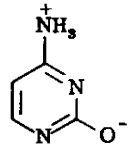
Sinsheimer *et al.*[156] measured the infrared spectra of pyrimidine



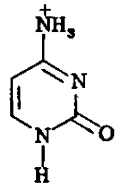
[*109*]



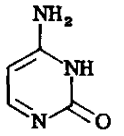
[*110*]



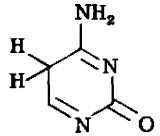
[*110a*]



[*110b*]



[*110c*]



[*111*]

[154] M. M. Stimson and M. J. O'Donnell, *J. Am. Chem. Soc.* **74**, 1805 (1952).
[154a] J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.* **83**, 2909 (1961).
[154b] A. R. Katritzky and A. J. Waring, *Chem. & Ind. (London)* p. 695 (1962).
[154c] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, in press.
[155] S. Y. Wang, *Nature* **184**, 184 (1959).
[156] R. L. Sinsheimer, R. L. Nutter, and G. R. Hopkins, *Biochim. et Biophys. Acta* **18**, 13 (1955).

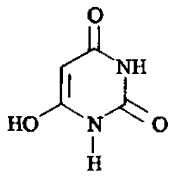
nucleotides in aqueous solution and concluded that the potential hydroxy compounds existed in the oxo form and amino compounds as such. The ionization of the ring protons was also discussed.[156] Similar work has been reported by Miles,[157] who compared the infrared and ultraviolet spectra of uridine and 3-methyluridine; uridine was thus shown to exist in the dioxo form, but thymidine was considered to exist, at least in part, in the monohydroxy form. From ultraviolet spectral evidence, Fox and Shugar[158] concluded that the tautomeric structures of the pyrimidine nucleosides closely resemble those of the corresponding alkylpyrimidine derivatives.

N. Barbituric Acid

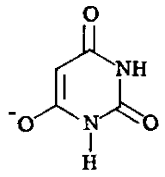
Early investigators adduced various kinds of chemical evidence in support of a monohydroxy–dioxo structure for barbituric acid (**112**): (a) reaction with diazomethane afforded a mono-*O*-methyl derivative,[159,160] (b) barbituric acid and its 5-alkyl derivatives are much stronger acids than the 5,5-dialkyl derivatives,[161] and (c) the 5-bromo and 5,5-dibromo derivatives have different chemical properties.[162] The early physical evidence also appeared to substantiate the monoenol structure, this formulation having been suggested for barbituric acid in 1926 on the basis of its ultraviolet spectrum[163] and again in 1934.[164] In the 1940's, ultraviolet spectroscopic studies led to the suggestion of other monohydroxy and dihydroxy structures for barbituric acid,[165] whereas its monoanion was assigned structure **113**[166–168] (a clear distinction between ionization and tautomerism was not made in these papers).

It has now become apparent that this early work had been incorrectly interpreted and that barbituric acid in fact exists predomi-

[157] H. T. Miles, *Biochim. et Biophys. Acta* **22**, 247 (1956).
[158] J. J. Fox and D. Shugar, *Biochim. et Biophys. Acta* **9**, 369 (1952).
[159] F. Arndt, *Rev. fac. sci. univ. Istanbul* **1**, 1 (1936).
[160] F. Arndt, *Rev. fac. sci. univ. Istanbul* **9A**, 19 (1944).
[161] J. K. Wood and E. A. Anderson, *J. Chem. Soc.* **95**, 979 (1909).
[162] G. W. Kenner and A. R. Todd, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, p. 257. Wiley, New York, 1957.
[163] A. K. Macbeth, T. H. Nunan, and D. Traill, *J. Chem. Soc.* p. 1248 (1926).
[164] F. F. Heyroth and J. R. Loofbourow, *J. Am. Chem. Soc.* **56**, 1728 (1934).
[165] J. R. Loofbourow and M. M. Stimson, *J. Chem. Soc.* p. 1275 (1940).
[166] R. E. Stuckey, *Quart. J. Pharm. and Pharmacol.* **15**, 370 (1942).
[167] R. E. Stuckey, *Quart. J. Pharm. and Pharmacol.* **15**, 377 (1942).
[168] R. E. Stuckey, *Quart. J. Pharm. and Pharmacol.* **13**, 312 (1940).

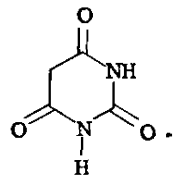


[112]



[113]

nantly in the trioxo form **114**. An equilibrium between the trioxo and monohydroxy-dioxo forms was postulated on the basis of ultraviolet spectral evidence in 1950,[169] and in 1952 Fox and Shugar, in a definitive paper,[170] demonstrated the predominance of the trioxo form. They further showed from the variation of the ultraviolet spectrum with pH that monoanion formation occurs by the loss of a proton attached to carbon and dianion formation by the loss of a second proton from a nitrogen atom. The trioxo formulation has recently been confirmed by X-ray crystallography[171,172] and by infrared spectroscopy.[112,173] A noncritical review of the tautomerism of barbituric acid is available.[174]

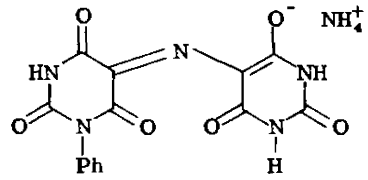


[114]

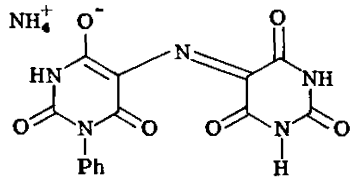
The isolation of unsymmetrically-substituted murexides in two forms, e.g., **115** and **116**, has been claimed (see reference **175** and

[169] O. Rosén and F. Sandberg, *Acta Chem. Scand.* **4**, 666 (1950).
[170] J. J. Fox and D. Shugar, *Bull. soc. chim. Belges* **61**, 44 (1952).
[171] S. Ghose, G. A. Jeffrey, B. M. Craven, and W. O. Warwicker, *Angew. Chem.* **72**, 754 (1960).
[172] S. Ghose, G. A. Jeffrey, B. M. Craven, and J. O. Warwicker, *Acta Cryst.* **13**, 1034 (1960).
[173] Y. Sata, K. Kotera, T. Takabashi, and T. Meshi, *Yakugaku Zasshi* **80**, 976 (1960).
[174] R. Y. Levina and F. K. Velichko, *Russ. Chem. Revs.* **29**, 437 (1960).
[175] N. M. Winslow, *J. Am. Chem. Soc.* **61**, 2089 (1939).

references therein), but a reinvestigation of these compounds using modern techniques would be welcome.



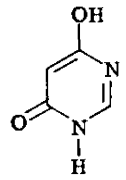
[115]



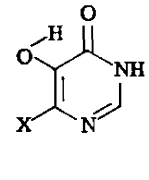
[116]

O. Other Potential 4,6-Dihydroxypyrimidines

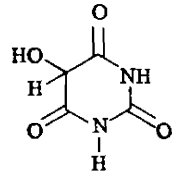
Tanner,[176] from infrared spectral work, tentatively concluded that 4,6- and 4,5-dihydroxy- and 4,5,6-trihydroxy-pyrimidines exist in the monooxo forms **117**, **118** (X = H), and **118** (X = OH), respectively; these conclusions are supported by ultraviolet spectral data and chemical evidence.[177] 2,4,5,6-Tetrahydroxypyrimidine has been isolated in two forms—dialuric acid and isodialuric acid, usually formulated as **119** and **120**, respectively, on the basis of rather convincing chemical evidence [for a review see reference **109(f)**; cf. reference **178**]. Isodialuric acid is converted into dialuric acid by base as would be expected if structures **119** and **120** are correct. On the basis of its infrared spectrum, dialuric acid has been concluded to exist in the tetrahydroxy form,[179] but the correctness of this conclusion appears very doubtful.



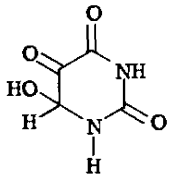
[117]



[118]



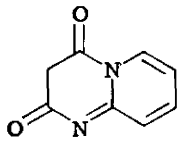
[119]



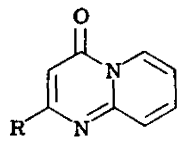
[120]

[176] E. M. Tanner, *Spectrochim. Acta* **8**, 9 (1956).
[177] J. Davoll and D. H. Laney, *J. Chem. Soc.* p. 2124 (1956).
[178] G. R. Ramage and J. K. Landquist, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, p. 1280. Elsevier, Amsterdam, 1959.
[179] R. S. Tipson and L. H. Cretcher, *J. Org. Chem.* **16**, 1091 (1951).

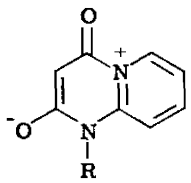
The structure of malonyl-α-aminopyridine (cf. **121**) has been discussed by Snyder and Robinson,[180] who interpreted the infrared and ultraviolet spectra and the fact that it could be converted into a monochloro derivative (**122**, R = Cl) to indicate that the intramolecularly hydrogen-bonded hydroxy form **122** (R = OH) was predominant. However, comparison of the basicities of the methoxy compound **122** (R = OMe), the mesomeric betaine **123** (R = Me), and the parent compound indicates that in aqueous solution the last exists mainly in the zwitterion form **123** (R = H).[181]



[*121*]



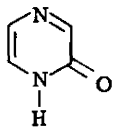
[*122*]



[*123*]

P. Pyrazinones and Quinoxalinones

Pyrazin-2-one (**124**) has been shown to exist predominantly as such by comparison of its ultraviolet spectrum with those of the fixed alkylated derivatives[68,111] and by its infrared spectrum.[53,112] The pK measurements support this conclusion but cannot yield quantitative results since cations of a common type are not formed.[111]

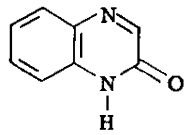


[*124*]

The predominance of the oxo forms of quinoxalin-2-one (**125**) and its 3-methyl derivative in aqueous solution was established by Cheeseman[183] using the pK method, only a lower limit being obtained for K_T (log $K_T > 1.6$ and 0.9, respectively) because similar cations are

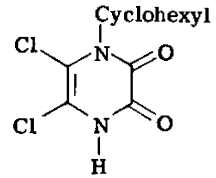
[180] H. R. Synder and M. M Robison, *J. Am. Chem. Soc.* **74**, 4910 (1952).
[181] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.* p. 1544 (1962).
[183] G. W. H. Cheeseman, *J. Chem. Soc.* p. 108 (1958).

not formed. Ultraviolet[183] and infrared spectral data[53,184,184a] further confirm the predominance of the oxo forms. Comparison of the ultraviolet spectrum of 3-styrylquinoxalin-2-one with that of the 1-phenyl derivative indicates that the former compound also exists in the oxo form.[185]

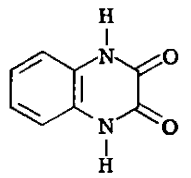


[*125*]

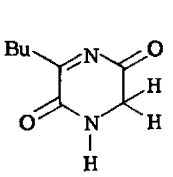
Little work has been reported on pyrazine-2,3-diones, however spectral evidence has been advanced by Honzl[186] to support the dioxo formulation **126**. Dioxo structures have been assigned to quinoxaline-2,3-dione (**127**) and its 1-methyl analog on the basis of ultraviolet[183] and infrared spectral data,[112,187] and according to



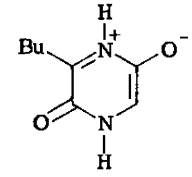
[*126*]



[*127*]



[*128*]



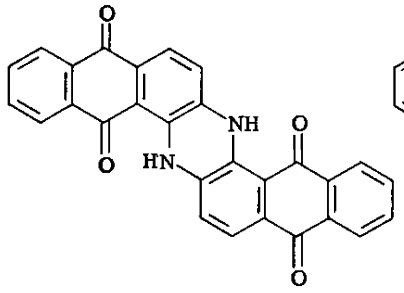
[*129*]

[184] Gj. Stefanović, L. J. Lorenc, and M. Lj. Mihailović, *Rec. trav. chim.* **80**, 149 (1961).
[184a] J. Derkosch, *Monatsh. Chem.* **92**, 1107 (1961).
[185] S. Bodforss, *Ann. Chem. Liebigs* **609**, 103 (1957).
[186] J. Honzl, *Collection Czechoslov. Chem. Communs.* **25**, 2653 (1960).
[187] G. W. H. Cheeseman, A. R. Katritzky, and S. Øksne, *J. Chem. Soc.* p. 3982 (1961).

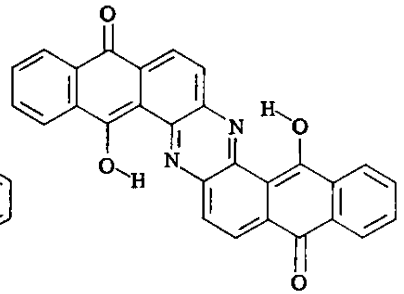
Sheĭnker and Pomerantsev[188] one of the protons remains bonded to a hetero nitrogen atom in the monoanion of **127**. 2,5-Dihydroxypyrazines could exist in a dioxo form (**128**) or in a zwitterion form (**129**), and, although structure **128** was assigned to the 5-butyl derivative in 1927,[189] the evidence for structure **128** as opposed to **129** is inconclusive.

Q. Indanthrone

The relative importance of structures **130** and **131** have long been discussed for the dye indanthrone. Initially, the infrared spectrum was considered to favor **131**[190] because a νN—H band could not be found. However, this interpretation has been questioned,[191] and recently the predominance of structure **130** was established by Weinstein and Merritt[192] on the basis of the following evidence: (*a*) a



[*130*]



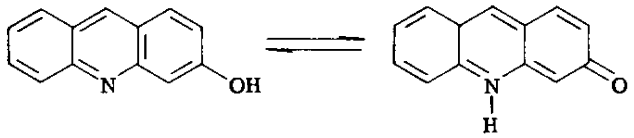
[*131*]

νNH band is present in the infrared spectra of both indanthrone and mono-*N*-methylindanthrone, (*b*) the infrared spectra of indanthrone and its mono- and di-*N*-methyl derivatives showed νC=O bands of approximately equal intensity, and (*c*) the ultraviolet and visible spectra of indanthrone and its *N*-methyl derivatives are similar.

[188] Yu. N. Sheĭnker and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* 33, 1819 (1959).
[189] E. Abderhalden and E. Rossner, *Z. physiol. Chem. Hoppe-Seyler's* 163, 149 (1927).
[190] G. M. Wyman, *J. Am. Chem. Soc.* 78, 4599 (1956).
[191] R. A. Durie and J. S. Shannon, *Australian J. Chem.* 11, 189 (1958).
[192] J. Weinstein and C. Merritt, *J. Am. Chem. Soc.* 81, 3759 (1959).

R. Pyridines and Azines in Which a Fused Benzene Ring or Phenyl Group Carries a Hydroxyl Group

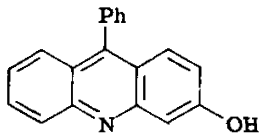
These compounds usually give many of the reactions characteristic of phenols and were long considered to exist completely in the hydroxy form (see, for example, reference 42). It has been noted that the ultraviolet spectra of aqueous ethanolic solutions of hydroxyacridines varied with changes in the composition of the solvent, and this phenomenon has been interpreted in terms of the equilibria **132** $\rightleftharpoons$ **133** and **134** $\rightleftharpoons$ **135**.[193-195] Some compounds of these types show interesting tautomeric phenomena in the solid state. Yellow crystals of the hydroxyacridine **136** are converted into a red powder when crushed, and Kehrmann and Matusinsky in 1912[196] attributed this color change to conversion of the hydroxy form into the oxo form **137**. This suggestion has recently been substantiated using ultraviolet spectroscopy,[194] the red form being a mixture of the tautomers, meta-



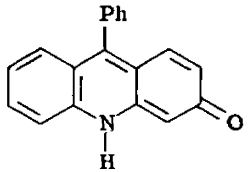
[*132*] [*133*]

[*134*] [*135*]

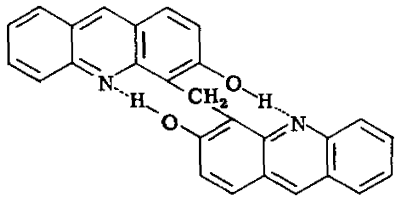
[193] A. Albert and L. N. Short, *J. Chem. Soc.* p. 760 (1945).
[194] N. Campbell and A. G. Cairns-Smith, *J. Chem. Soc.* p. 1191 (1961).
[195] A. I. Gurevich and Yu. N. Sheinker, *Zhur. Fiz. Khim.* 33, 883 (1959).
[196] F. Kehrmann and Z. Matusinsky, *Ber. deut. chem. Ges.* 45, 3498 (1912).



[136]

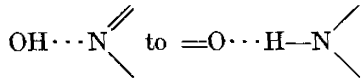


[137]



[138]

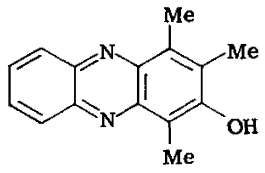
stable at all temperatures, and probably produced during the grinding because of local melting and a randomization of the lattice hydrogen bonds from



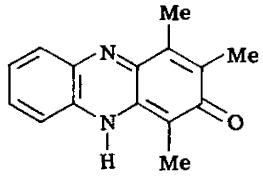
Support for this theory is given by the thermochromism of hydroxyacridines of type **138** and the corresponding phenazine compounds.[197]

Osborn and Schofield[198] reported that the hydroxycinnolines are in equilibrium with small amounts of the zwitterion form. In 1946, 2-hydroxy-1,3,4-trimethylphenazine was isolated in two forms, a blue-red and a yellow form, which were assigned structures **139** and **140**[199] (see also reference 200). Ethanolic solutions of 2-hydroxyphenazine are yellow (resembling 2-methoxyphenazine), and the color intensifies in aqueous solution corresponding to absorption at longer wavelengths and indicating the presence of form **141**.[201] This effect is not observed for 1-hydroxyphenazine, probably because structure **142** is stabilized by hydrogen bonding. In the solid state, **143** probably exists as

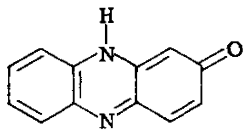
[197] A. G. Cairns-Smith, *J. Chem. Soc.* p. 182 (1961).
[198] A. R. Osborn and K. Schofield, *J. Chem. Soc.* p. 4207 (1956).
[199] W. John, *Angew. Chem.* **59**, 188 (1947).
[200] H. H. Perkampus, *Z. physik. Chem. (Frankfurt)* **6**, 18 (1956).
[201] G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.* p. 3204 (1951).



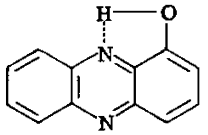
[139]



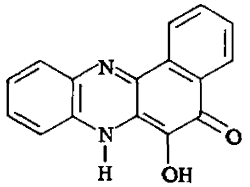
[140]



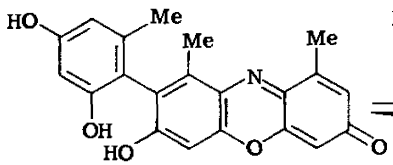
[141]



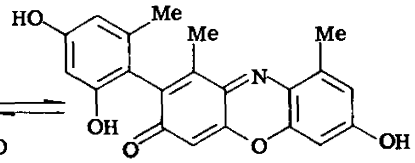
[142]



[143]



[144]



[145]

shown.[201] The tautomerism of hydroxyphenazones is important in the orcein dyes, e.g., α-hydroxyorcein (**144** ⇌ **145**; see references 202 and references therein).

A systematic investigation of compounds of these types by Mason[53,60,68] has recently placed this subject on a firm basis. The infrared spectra of chloroform and carbon tetrachloride solutions of

[202] H. Musso and H. Beecken, *Chem. Ber.* **94**, 585 (1961).

TABLE IV

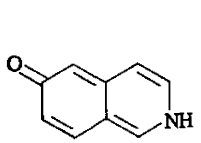
RATIO OF ZWITTERION FORM TO HYDROXY FORM (pK_T) FOR PYRIDINES AND AZINES IN WHICH A BENZO RING CARRIES A HYDROXYL GROUP

Compound	pK Method[a]	UV Method[b]	IR Method[c,d]	Quinonoid form[e]
5-Hydroxyquinoline	−0.86	−1.27	pr	di-*ortho*
6-Hydroxyquinoline	−2.09	−1.85	pr	—
7-Hydroxyquinoline	0.69	−3.07	pr	*ortho-para*
8-Hydroxyquinoline	−1.67	−1.46	pr	—
5-Hydroxyisoquinoline	−1.45	−1.42	pr	—
6-Hydroxyisoquinoline	0.32	0.28	pr	di-*para*
7-Hydroxyisoquinoline	−1.37	−1.42	pr	—
8-Hydroxyisoquinoline	0.38	−0.06	pr	*para-ortho*
1-Hydroxyacridine	−1.6	−1.44	pr	di-*ortho*
2-Hydroxyacridine	—	0.40	—	—
3-Hydroxyacridine	0.8	−1.82	pr	*ortho-para*
4-Hydroxyacridine	—	−0.48	pr	—
7-Hydroxyphenanthridine	—	<-1	pr	—
5-Hydroxyquinoxaline	−4.8	—	pr	*ortho-para*
6-Hydroxyquinoxaline	—	—	pr	—
8-Hydroxyquinoxaline	−3.85	—	—	—
1-Hydroxyphenazine	−3.5	—	pr	*ortho-para*
2-Hydroxyphenazine	−0.2	$\geqslant -0.6$	pr	*para-para*
5-Hydroxycinnoline	—	—	pr[f]	—
6-Hydroxycinnoline	—	$\geqslant 0.1$	pr[f]	—
7-Hydroxycinnoline	—	$\geqslant 0.03$	pr[f]	—
8-Hydroxycinnoline	—	$\geqslant 0.004$	pr	—
6-Hydroxyphthalazine	—	$\geqslant 0.1$	pr[f]	—
2-Hydroxyphenanthridine	—	$\leqslant 0.001$	pr	—
6-Hydroxyphenanthridine	—	$\leqslant 5$	pr	—
7-Hydroxyphenanthridine	—	$\leqslant 0.1$	pr	—
6-Hydroxyquinazoline	—	—	pr	—
8-Hydroxyquinazoline	—	—	pr	—
1-Hydroxyphenazine	—	—	pr	—
2-Hydroxyphenazine	—	—	pr	—

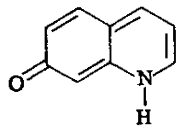
[a] S. F. Mason, *J. Chem. Soc.* p. 674 (1958).
[b] S. F. Mason, *J. Chem. Soc.* p. 5010 (1957).
[c] S. F. Mason, *J. Chem. Soc.* p. 4874 (1957).
[d] In this column "pr" indicates the predominance of the hydroxyl form.
[e] The type of extended quinonoid form (cf. **133**), if any, which can stabilize the zwitterion form is shown.
[f] Solid state spectra only, otherwise chloroform or carbon tetrachloride solution.

these compounds indicate that they exist predominantly in the hydroxy form,[53] whereas the ultraviolet spectra measured in solvents of low dielectric constant, for example, dioxane and ethanol, closely

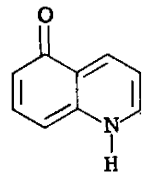
resemble those of the *O*-methyl derivatives, again showing the predominance of the hydroxy form.[68] However, in aqueous solution, ultraviolet absorption bands corresponding to the *N*-methyl derivatives appear, demonstrating that under these conditions the hydroxy and zwitterion forms are in equilibrium. This conclusion was confirmed by pK_a measurements on the potentially tautomeric compounds and the alkylated derivatives of both forms.[60] The tautomeric constants calculated by both methods are given in Table IV and show satisfactory agreement. The proportion of a given compound which occurs in the NH form depends upon the possibilities for conjugation between the oxygen and nitrogen atoms.[68] This conjugation is most effective for transannular *"para-para"* quinonoid structures (e.g., **146**), successively less for *"para-ortho"* (e.g., **147**) and *"ortho-ortho"* structures (e.g., **148**), and least when no uncharged form can be written for the NH form (e.g., **149**). The fact that additional fused benzene rings generally tend to stabilize the NH form (cf. **150**) has been attributed



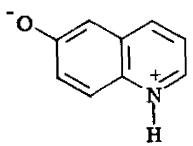
[146]



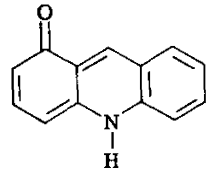
[147]



[148]



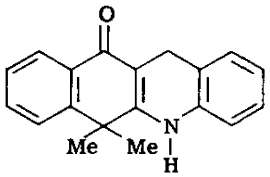
[149]



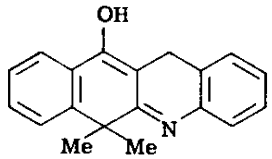
[150]

to the relatively less important loss of benzenoid resonance in the uncharged NH cannonical form. The effect of temperature in decreasing the amount of the NH form present at equilibrium was mentioned in Section I,E, of the preceding article I by Katritzky and Lagowski, and, using these results, the heat content and the entropy changes for the reactions were calculated.[68]

The tautomeric equilibrium **151** ⇌ **152** has been discussed by Cromwell and David.[203] Ultraviolet spectral data indicate that **151** predominates in neutral aqueous solution, and infrared data are in essential agreement. It was further concluded that in acid solution the equilibrium favors **152**, but no ionization constants were reported,



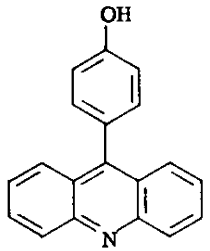
[*151*]



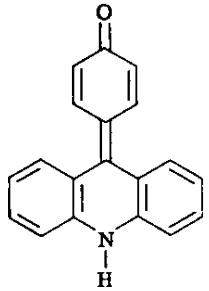
[*152*]

and the processes of cation formation and tautomerism do not appear to have been clearly distinguished in this study. For an early discussion of 8-hydroxyquinoline with respect to its ultraviolet spectrum and ionization constants, see reference 204.

9-*p*-Hydroxyphenyl- (**153**) and 9-*p*-hydroxystyryl-acridine have been reported to exist as such and not as the "extended quinones" (cf. **154**) on the basis of polarographic[205] and spectral evidence.[206,207]



[*153*]

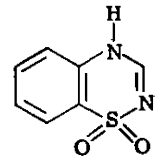


[*154*]

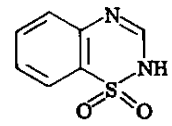
[203] N. H. Cromwell and J. C. David, *J. Am. Chem. Soc.* **82**, 2046 (1960).
[204] K. G. Stone and L. Friedman, *J. Am. Chem. Soc.* **69**, 209 (1947).
[205] N. F. Kazarinova and I. Ya. Postovskiĭ, *J. Gen. Chem. U.S.S.R.* (*Eng. Trans.*) **27**, 3325 (1957).
[206] Yu. N. Sheĭnker and I. Ya. Postovskiĭ, *Zhur. Fiz. Khim.* **32**, 394 (1958).
[207] V. Zanker and A. Reichel, *Z. Elektrochem.* **64**, 431 (1960).

S. Benzo-1,2,4-thiadiazine 1,1-Dioxides

Comparison of the ultraviolet spectra of the parent compounds with those of both possible *N*-methyl derivatives shows that the Δ^2 structures (cf. **155**) predominate in equilibria of type **155** ⇌ **156**.[208]



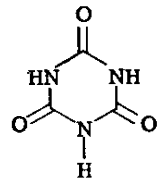
[*155*]



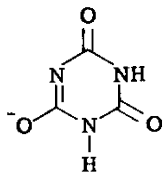
[*156*]

T. Triazinones

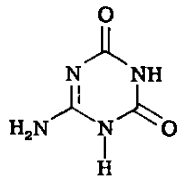
The ultraviolet[209] and infrared spectra[112,210,211] and the crystal structure (as determined by X-rays)[212] of cyanuric acid have been interpreted on the basis of the trioxo structure **157**; however, other ultraviolet data have been reported from which it was concluded that approximately 5% of this compound exists in a hydroxy form in solution.[213] The monoanion of cyanuric acid exists as **158**.[188] Ultraviolet spectral data suggest that ammelide (**159**) and ammeline (**160**) exist as shown[214] (available infrared spectra offer less conclusive evi-



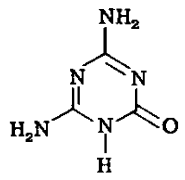
[*157*]



[*158*]



[*159*]



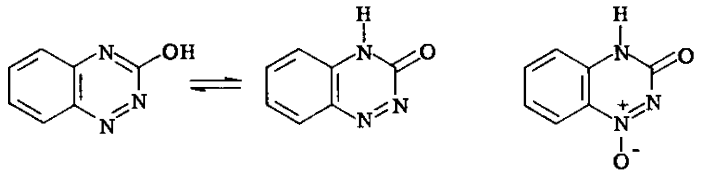
[*160*]

[208] F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.* **25**, 970 (1960).
[209] I. M. Klotz and T. Askounis, *J. Am. Chem. Soc.* **69**, 801 (1947).
[210] R. Newman and R. M. Badger, *J. Am. Chem. Soc.* **74**, 3545 (1952).
[211] W. M. Padgett and W. F. Hamner, *J. Am. Chem. Soc.* **80**, 803 (1958).
[212] E. H. Wiebenga and N. F. Moerman, *Z. Krist.* **99**, 217 (1938).
[213] E. Agallidis, H. Fromberz, and A. Hartmann, *Ber. deut. chem. Gez.* **71**, 1391 (1938).
[214] R. C. Hirt and R. G. Schmitt, *Spectrochim. Acta* **12**, 127 (1958).

dence[211]); the structure of the ionized forms has also been discussed.

s-Triazine-2,4-dione (5-azauracil) exists in the dioxo form (cf. chapter by Gut, Section I,A,2,b),

If diazomethane is added slowly to an etheral suspension of benzo-1,2,4-triazin-3-one, the *O*-methyl derivative (cf. **161**) is obtained in good yield, but, if the solid benzotriazinone is added to an etheral solution of diazomethane, approximately 50% of the *N*-methyl derivative (or, according to a later report,[215] 70% of a mixture of two isomeric *N*-methyl derivatives) is formed.[216] These facts have been interpreted to indicate that the benzotriazinone exists as such in the solid state, i.e., as **162**, and partially tautomerizes to **161** in solution.[216] Similar results have been reported and similar conclusions drawn for the related 1-oxide **162a**.[215]



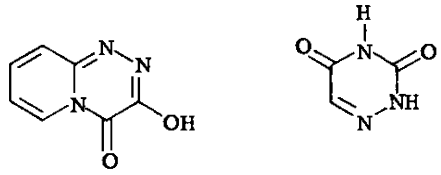
[*161*] [*162*] [*162a*]

In a preliminary communication, the dihydroxy-1,2,4-triazine derivative **163** has been assigned the structure shown on the basis of infrared evidence.[217] The pK[218] and ultraviolet[219] and infrared spectral data[220] support the formulation of "6-azauracil" (**164**) as a dioxo compound.

U. Oxotriazanaphthalenes

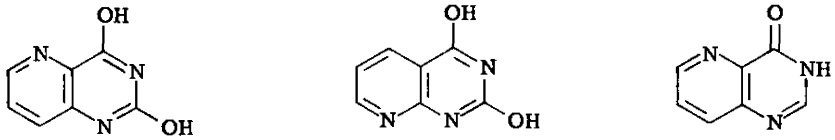
2,4-Dihydroxy-1,3,5- and -1,3,8-triazanaphthalene have been reported to exist as diols **165** and **166**, respectively, since their ultraviolet

[215] L. Ergener, *Rev. fac. sci. univ. Istanbul* **15A**, 91 (1950).
[216] F. Arndt, *Angew. Chem.* **61**, 397 (1949).
[217] T. Kauffmann, H. Hacker, C. Kosel, and K. Vogt, *Z. Naturforsch.* **14b**, 601 (1959).
[218] J. Gut, M. Prystaš, J. Jonáš, and F. Šorm, *Collection Czechoslov. Chem. Communs.* **26**, 1681 (1961).
[219] J. Jonáš and J. Gut, *Collection Czechoslov. Chem. Communs.* **26**, 2155 (1961).
[220] M. Horák and J. Gut, *Collection Czechoslov. Chem. Communs.* **26**, 1681 (1961).



[*163*] [*164*]

spectra were more similar to those of the dimethoxy derivatives than to those of the di-*N*-methyl compounds.[221] The present authors feel, however, that these ultraviolet spectra are too similar to permit an unambiguous decision and that the monooxo forms should have been



[*165*] [*166*] [*167*]

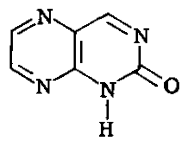
taken into consideration. Infrared spectral data suggest that 4-hydroxy-1,3,5-triazanaphthalene exists predominantly in the oxo form **167**,[53] and it is highly probable that the oxo forms of **165** and **166** also predominate.

V. Pteridinones

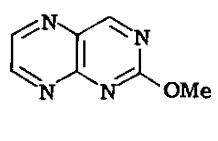
1. *Monooxo Derivatives*

The monohydroxypteridines have been shown[222-224] to exist predominantly in the oxo forms, but complex equilibria are nevertheless present; for example, pteridin-2-one (**168**) can exist in four tautomeric forms.[225] Comparison of the ultraviolet spectra of methyl derivatives corresponding to these four forms (i.e., **169–172**) with that of the

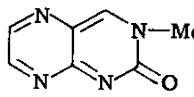
[221] V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.* p. 1045 (1956).
[222] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* p. 1620 (1952).
[223] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* p. 4219 (1952).
[224] D. J. Brown and S. F. Mason, *J. Chem. Soc.* p. 3443 (1956).
[225] Paper chromatographic separation of two forms of 4,6-dihydroxypteridine has been reported [A. Albert and D. J. Brown, *J. Chem. Soc.* p. 74 (1953)], but this should be further investigated.



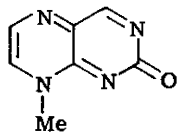
[168]



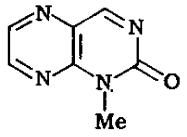
[169]



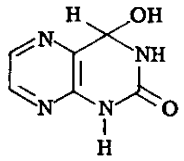
[170]



[171]



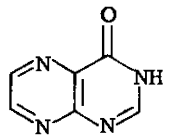
[172]



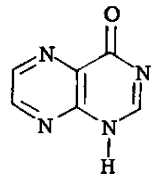
[173]

potentially tautomeric compound showed that it exists in the anhydrous state as **168**, whereas the hydrated form is probably **173**.

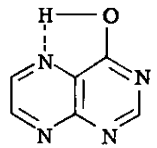
Ultraviolet spectral comparisons also indicate that structure **174** represents the predominant form of pteridin-4-one (a similar conclusion was reached for 2-amino-6,7-dimethylpteridin-4-one[226]), and a value of 1.72 has been calculated for log K_{op} between forms **174** and **175** from pK_a data.[60] It is possible, however, that the hydroxy



[174]



[175]



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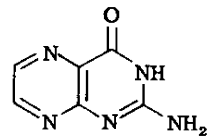
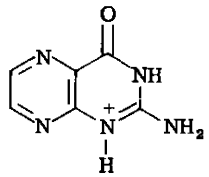


[177]

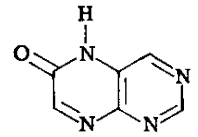


[178]

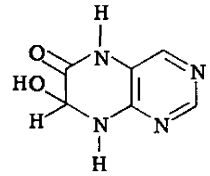
[223] R. B. Angier and W. V. Curran, *J. Org. Chem.* **26**, 2129 (1961).

form (**176**), which may be stabilized by hydrogen bonding, is present in an appreciable proportion. Ultraviolet spectra and basicity data indicate that the natural product pterin exists predominately as **177** and its monocation as **178**.[227]

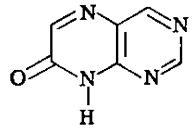
Pteridin-6-one (**179**) is probably hydrated in aqueous solution and, therefore, best represented by structure **180**.[224] Ultraviolet spectral comparisons and infrared data support the oxo formulation for pteridin-7-one (**181**).



[179]



[180]



[181]

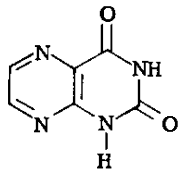
For a discussion of aminopteridinones, see Section IV,G.

2. *Polyoxo Derivatives*

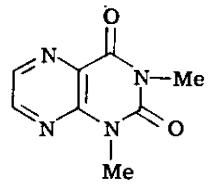
The structures of many polyhydroxypteridines have been investigated by Pfleiderer and his associates.[228–234] Although 2,4-dihydroxypteridine (lumazine) appears to exist mainly in the dioxo form **182**,

[227] W. Pfleiderer, E. Liedek, R. Lohrmann, and M. Rukwied, *Chem. Ber.* **93**, 2015 (1960).
[228] W. Pfleiderer, *Chem. Ber.* **90**, 2582 (1957).
[229] W. Pfleiderer, *Chem. Ber.* **90**, 2588 (1957).
[230] W. Pfleiderer, *Chem. Ber.* **90**, 2604 (1957).
[231] W. Pfleiderer, *Chem. Ber.* **90**, 2617 (1957).
[232] W. Pfleiderer, *Chem. Ber.* **90**, 2624 (1957).
[233] W. Pfleiderer, *Chem. Ber.* **90**, 2631 (1957).
[234] W. Pfleiderer and M. Rukwied, *Chem. Ber.* **94**, 1 (1961).

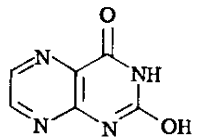
the similarity of the ultraviolet spectra of both the di-*N*-methyl and the di-*O*-methyl derivatives preclude a conclusive decision on this basis.[228] On reaction with diazomethane only the di-*N*-methyl derivative **183** is formed. Lippert and Prigge[235] made a careful study of the



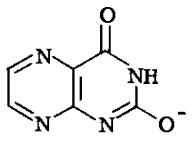
[*182*]



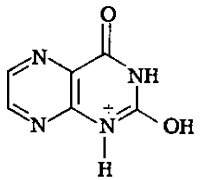
[*183*]



[*184*]



[*185*]



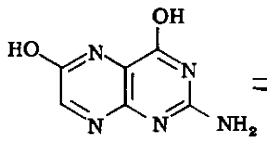
[*186*]

ultraviolet and fluorescence spectra and pK values of lumazine and its methylated derivatives, which shows that in the ground state and in the first excited state the molecule exists in the dioxo form with a small contribution from **184** ($pK_T = 1.88$, $pK_T^* = 4.3$) and that the monoanion and monocation exist as **185** and **186**, respectively. A dioxo structure has also been assigned to 6,7-diethylpteridine-2,4-dione on the basis of its infrared spectrum.[53]

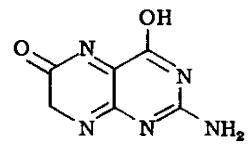
2,6-[236] and 4,6-Dihydroxypteridine[237] on titration with alkali followed by back titration with acid show hysteresis suggesting that covalent hydration takes place in these derivatives, the products probably having structures similar to **180**. Before it was realized that covalent hydration could account for this hysteresis, it was tentatively attributed to a slow tautomerism.[238] The peculiar chromatographic

[235] E. Lippert and H. Prigge, *Z. Elektrochem.* **64**, 662 (1960).
[236] A. Albert, J. H. Lister, and C. Pedersen, *J. Chem. Soc.* p. 4621 (1956).
[237] A. Albert and D. J. Brown, *J. Chem. Soc.* p. 74 (1953).
[238] A. Albert, *in* "Chemistry and Biochemistry of Pteridines" (G. E. W. Wolstenholme and M. P. Cameron, eds.), p. 210. Churchill, London, 1954.

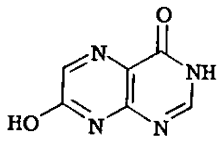
behavior of xanthopterin (2-aminopteridine-4,6-dione)[239] can probably be attributed to covalent hydration also.[236] An equilibrium between **187** and **188** has been postulated from ultraviolet data,[240] but



[*187*]



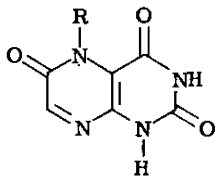
[*188*]



[*189*]

the argument is not convincing and the conclusions seem improbable. 4,7-Dihydroxypteridine has been assigned the monohydroxy-monooxo structure **189**[241,242]; however, 2-amino-4,7-dihydroxypteridine (isoxanthopterin) exists in the dioxo form.[234]

The trioxo formulation (**190**, R = H) of 2,4,6-trihydroxypteridine is supported by the fact that its ultraviolet spectrum resembles that of the *N*-methyl derivative (**190**, R = Me), the pyrimidine ring in the parent compound having been assigned the dioxo configuration by analogy.[230] On the basis of ultraviolet spectral data, the trioxo con-

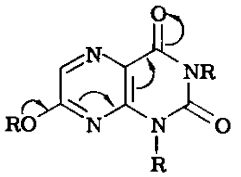


[*190*]

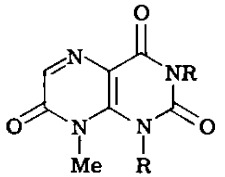
figuration has also been suggested for pteridine-2,4,6-trione-7-carboxylic acid[232] and for 2-aminopteridine-4,6,7-trione (leucopterin).[243]

[239] R. Tschesche and F. Korte, *Chem. Ber.* **85**, 139 (1952).
[240] M. A. Schou, *Arch. Biochem.* **28**, 10 (1950).
[241] W. Pfleiderer, *Chem. Ber.* **92**, 3190 (1959).
[242] Pteridines which carry a hydroxyl group are appreciably acidic and react rapidly with diazomethane to yield *O*-methyl derivatives; this, of course, means that the alternative NH form must be still more strongly acidic because the most stable tautomer is always the weakest acid.
[243] W. Pfleiderer and M. Rukwied, *Chem. Ber.* **94**, 118 (1961).

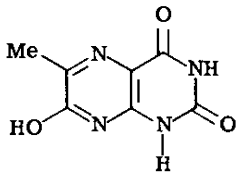
2,4,7-Trihydroxypteridine exists predominantly in the dioxo-monohydroxy form **191**(R = H),[229] its ultraviolet spectrum closely resembling those of both the 1- and the 3-methyl derivatives and that of 1,3-dimethyl-7-methoxypteridine-2,4-dione (**191**, R = Me). These spectra are quite different from those of 8-methyl- (**192**, R = H) and 1,3,8-trimethyl-pteridine-2,4,7-trione (**192**, R = Me), which are similar to each other and to those of other 8-substituted pteridine-2,4,7-triones.[244] However, the ultraviolet spectrum of 2,4,7-trihydroxypteridine does, indeed, show that a small proportion of the trioxo form is present at equilibrium. A somewhat larger proportion of the 6-methyl derivative exists in the trioxo form, although structure **193** predominates. The trioxo form (**194**) of 2,4,7-trihydroxy-1,3,6-trimethylpteridine is the most important tautomer, but the corresponding 6-carboxylic acid exists entirely in the monohydroxy-dioxo form **195**.[231]



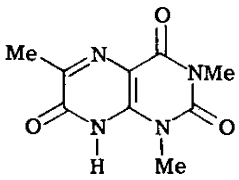
[*191*]



[*192*]



[*193*]



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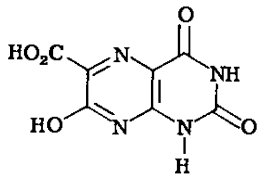
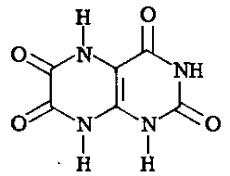


[*195*]

[244] W. Pfleiderer and G. Nübel, *Chem. Ber.* **93**, 1406 (1960).

Pfleiderer has suggested that the 7-hydroxy group exists as such in these compounds because this form is stabilized by mesomerism of type **191** (R = H). The tautomerism of 7-hydroxypteridine-2,4-dione in the excited electronic state has been studied on the basis of its fluorescence spectrum.[244a]

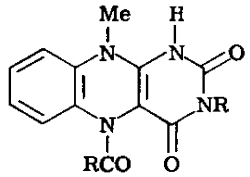
Somewhat surprisingly, it appears that 2,4,6,7-tetrahydroxypteridine exists in the tetraoxo form (**196**) since its ultraviolet spectrum is similar to those of the 1-, 3-, and 8-monomethyl derivatives and to that of the 1,3,5,8-tetramethyl derivative.[233]



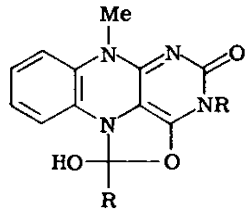
[*196*]

W. Flavin Derivatives

Tautomerism of type **197** ⇌ **198** has been postulated to occur in flavin derivatives on the basis of infrared spectral data.[245]



[*197*]



[*198*]

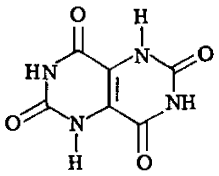
X. Other Oxotetraazanaphthalenes

Fischer and Neumann[246] have discussed the ultraviolet and fluorescence spectra of **199** and **200** and consider them to support the polyoxo forms shown.

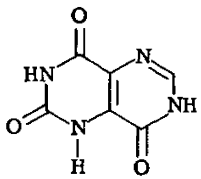
[244a] E. Lippert, W. Lüder, F. Moll, W. Nägele, H. Boos, H. Prigge, and I. Seibold-Blankenstein, *Angew. Chem.* **73**, 695 (1961).

[245] P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta* **43**, 372 (1960).

[246] F. G. Fischer and W. P. Neumann, *Ann. Chem. Liebigs* **572**, 230 (1951).



[199]



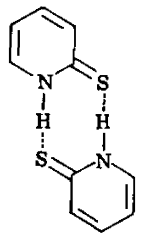
[200]

III. Compounds with Potential Mercapto Groups

The acidic properties of mercapto groups are considerably more pronounced than those of hydroxy groups, and reasoning from the relative stabilities of the oxo–zwitterion forms and the hydroxy forms, the thione–zwitterion forms would be expected to be more stable than the mercapto forms. However, the stability of thione groups is less than that of carbonyl groups (owing to the disinclination of sulfur to form π-bonds; cf. the discussion in reference 247 and references therein), and on the whole the two effects appear largely to cancel one another. Thus, the mercapto-thione tautomerism of heterocyclic compounds is similar to that exhibited by the oxygen analogs, the thione form usually being slightly more favored than the corresponding oxo form.

A. Pyrid-2- and -4-thiones

In 1951, pyrid-4-thione was concluded from ultraviolet spectral data to exist predominantly as such in ethanolic solution,[248] but no comparisons were made and this conclusion had to be considered as tentative. Pyrid-2-thione has been shown by X-ray crystallography to exist as hydrogen-bonded dimers (**201**) in the solid state, the positions of the hydrogen atoms being deduced from the measured bond lengths between the heavy atoms.[249] Absorption bands corresponding to neither NH nor SH stretching frequencies were found in the solid-state infrared spectrum of pyrid-2-thione, although a mixture of the forms was considered to exist in solution since reaction with diazomethane gave both the *N*-methyl and the S-methyl derivatives, with the latter predominating.[250]



[201]

[247] W. H. R. Shaw and D. G. Walker, *J. Am. Chem. Soc.* **80**, 5337 (1958).
[248] I. G. Ross, *J. Chem. Soc.* p. 1374 (1951).

English and Australian investigators[251–253] showed simultaneously that the pyrid-2- and -4-thione forms predominate in aqueous solution by factors of ca. 10^4 (see Table V) by comparative studies of these compounds and the alkylated derivatives of both forms using pK_a data; these conclusions are supported by ultraviolet spectral comparisons. Detailed analyses of the infrared spectra of pyrid-2- and -4-thione indicate that the thione forms greatly predominate both

TABLE V
Ratio of the Thione to the Mercapto Forms (pK_T)[a]

Position of SH group	Ring system	pK_T
2	Pyridine	4.7[b]
3	Pyridine	2.2
4	Pyridine	4.5[c]
1	Isoquinoline	5.8
3	Isoquinoline	3.0
2	Quinoline	5.1
3	Quinoline	1.5
4	Quinoline	5.0
5	Quinoline	1.2
6	Quinoline	0.7
8	Quinoline	1.4

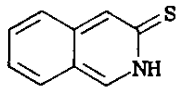
[a] All values taken from A. Albert and G. B. Barlin, *J. Chem. Soc.* p. 2384 (1959).
[b] Jones and Katritzky [*J. Chem. Soc.* p. 3610 (1958)] give a value of 4.0.
[c] Jones and Katritzky [*J. Chem. Soc.* p. 3610 (1958)] give a value of 4.6.

[249] B. R. Penfold, *Acta Cryst.* **6**, 707 (1953).
[250] J. Renault, *Ann. chim. (Paris)* **10**, 135 (1955).
[251] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* p. 3610 (1958).
[252] A. Albert and G. B. Barlin, *J. Chem. Soc.* p. 2384 (1959).
[253] A. Albert and G. B. Barlin, *in* "Symposium on Current Trends in Heterocyclic Chemistry" (A. Albert, G. M. Badger, and C. W. Shoppee, eds.), p. 51. Butterworths, London, 1958.

in chloroform solution and in the solid state.[51,254,255] Further ultraviolet spectral comparisons, leading to the same conclusions, have been made by Russian workers.[255a]

B. Quinol-2- and -4-thiones and Isoquinol-1- and -3-thiones

In 1939, the ultraviolet spectrum of 4-methylquinol-2-thione was reported to differ from that of the 2-alkylthio analog, and the former compound was concluded to exist in the thione form.[256] However, other investigators were unable to reach any conclusions from ultraviolet and infrared spectral data concerning the tautomerism of quinol-2- and -4-thione.[257] A definitive pK and ultraviolet spectral investigation by Albert and Barlin[252] has recently established that the thione forms of quinol-2- and -4-thione and of isoquinol-1- and -3-thione (cf. **202**) greatly predominate (Table V). The infrared

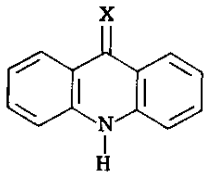


[*202*]

spectra of quinol-2- and -4-thione and isoquinol-1-thione[254] further support the predominance of the thione form.

C. Acridan-9-thione

The colors of acridan-9-thione and -9-selenone (**203**, X = S, Se) are



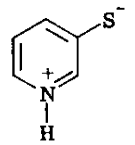
[*203*]

[254] E. Spinner, *J. Chem. Soc.* p. 1237 (1960).
[255] E. Spinner, *J. Org. Chem.* **23**, 2037 (1958).
[255a] V. S. Korobkov, A. V. Voropaeva, and I. H. Feldman, *Zhur. Obshei. Khim.* **31**, 3136 (1961).
[256] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.* p. 1321 (1939).
[257] R. B. Hannen, J. H. Liebich, and A. G. Renfrew, *J. Am. Chem. Soc.* **71**, 3733 (1949).

similar to those of their N-methyl derivatives, and this observation was advanced in 1939 as evidence for the predominance of the thione and selenone forms.[258] Acridan-9-thione, which is associated, has been considered by Hopkins and Hunter[259] to be an example of "mesohydric tautomerism" (cf. Section I,C, of article I by Katritzky and Lagowski). Ultraviolet spectral comparisons of the parent compound with both the alkylated forms have established that the former exists overwhelmingly in the thione form.[260]

D. β-Mercaptopyridines

3-Mercaptopyridine and 3-mercaptoquinoline have been shown to exist predominantly in the zwitterion form (e.g., **204**) by ultraviolet spectral comparisons and pK measurements[252] (cf. Table V).



[*204*]

E. 1-Hydroxypyridthiones (Mercaptopyridine 1-Oxides)

1-Hydroxypyrid-2- and -4-thione are weaker bases than 2- and 4-benzylthiopyridines, respectively.[261] Alkylation probably has very little effect on the basicity, and these results thus show that in the 2- and 4-series the thione form is preferred by factors of approximately 50 and 4, respectively. Ultraviolet[261] and infrared spectral data[51] also indicate that the thione forms of these compounds predominate, which is in accord with the general pattern of tautomeric equilibria. In exact analogy with the hydroxypyridines and their 1-oxides (cf. Section II,F), introduction of the N-oxide oxygen atom increases the mesomeric stabilization of the mercaptopyridine 1-oxide form and decreases that of the 1-hydroxypyridthione form, with the result that the equilibrium is much less in favor of the thione form than in the case of the mercaptopyridines themselves.

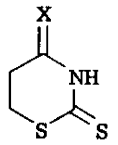
[258] K. Gleu and R. Schaarschmidt, *Ber. deut. chem. Ges.* **72**, 1246 (1939).
[259] G. Hopkins and L. Hunter, *J. Chem. Soc.* p. 638 (1942).
[260] R. M. Acheson, M. L. Burstall, C. W. Jefford, and B. F. Sansom, *J. Chem. Soc.* p. 3742 (1954).
[261] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2937 (1960).

F. Quinolines Carrying a Mercapto Group on the Benzo Ring

Mercaptoquinolines of this type exist in the zwitterion or the zwitterion–extended quinone form to a greater extent than do the analogous hydroxy compounds[252] (see Table V and Section II,R), and the color of 8-mercaptoquinoline has been attributed to the zwitterion structure.[262] The concentration of the zwitterion decreases as the dielectric constant of the solvent decreases in the order $H_2O > MeOH > EtOH > Bu^tOH$ as indicated by the change in the molecular extinction coefficient.[263]

G. Thiazinethiones

Ultraviolet spectroscopic comparisons have established the thione structures for **205** (X = H_2)[264] and **205** (X = O).[265]

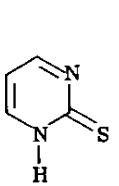


[205]

H. Diazinethiones

Pyrimidine-2-thiones (e.g., **206**) have been shown to exist as such by comparison of their ultraviolet spectra with those of both alkylated forms.[134,135] The ultraviolet spectra of pyrimidine-4-thiones are different from those of 4-alkylthiopyrimidines, therefore the former compounds exist as **207** and/or **208**,[134,135] the predominant form not having been determined. Infrared spectral evidence suggests that quinazoline-4-thione exists as **209** and/or **210**[143] and has been used recently to demonstrate the thione formulation for pyrimidine-2- and -4-thione, pyrazine-2-thione, and quinoxaline-2-thione.[254] In view of this work, the report[266] that X-ray crystallographic evidence supports the mercapto formulation of 4-mercapto-2,5-diamino-6-methylpyrimidine must be viewed with caution.

[262] J. E. Banfield, *J. Org. Chem.* **25**, 300 (1960).
[263] H.-S. Lee and H. Freiser, *J. Org. Chem.* **25**, 1277 (1960).
[264] F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.* p. 243 (1943).
[265] M. Tišler, *Arch. Pharm.* **294**, 348 (1961).
[266] E. N. Maslen, D. E. Jukes, and C. J. B. Clews, *Acta Cryst.* **11**, 115 (1958).



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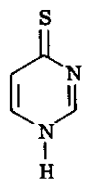

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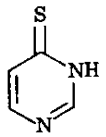
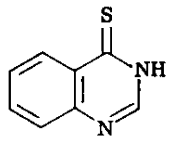
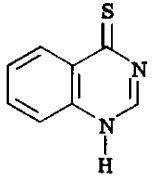


[208]

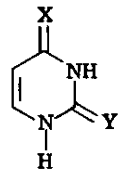


[209]

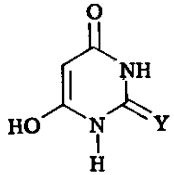


[210]

The tautomerism of the thiouracils has been discussed with reference to their ultraviolet spectra.[267] Dipole moment studies of the mono- and di-thiouracils (**211**; X, Y = O, S) and their various alkyl derivatives indicate that they all exist in the dioxo, oxothio, or dithione form,[268] and this has been confirmed by X-ray studies[269] and, in the case of 2-thiouracil, by nuclear magnetic resonance spectroscopy.[139] The pK_a data were taken to indicate that 2-thio- and 2-seleno-barbituric acid can be assigned structure **212** (Y = S, Se)[270];



[211]

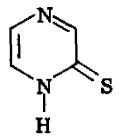


[212]

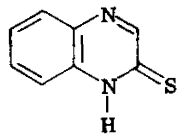
[267] G. B. Elion, W. S. Ide, and G. H. Hitchings, *J. Am. Chem. Soc.* **68**, 2137 (1946).
[268] W. C. Schneider and I. F. Halverstadt, *J. Am. Chem. Soc.* **70**, 2626 (1948).
[269] G. S. Parry and F. Strachan, *Acta Cryst.* **13**, 1035 (1960).
[270] H. G. Mautner and E. M. Clayton, *J. Am. Chem. Soc.* **81**, 6270 (1959).

see, however, the discussion of barbituric acid in Section II,N.

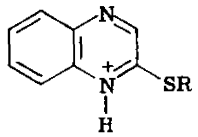
Pyrazine-2-thione (**213**)[111] and quinoxaline-2-thione (**214**)[183] probably exist in the thione form since their ultraviolet spectra are different from those of the 2-methylthio analogs. The basicity of quinoxaline-2-thione is 1.4 pK units less than that of 2-methylthioquinoxaline, and the ultraviolet spectra of the cations are dissimilar. Presumably quinoxaline-2-thione and its 2-methylthio derivative do not form similar cations (**215**, R = alkyl, H), and it would appear that either the thione gives the cation **216** or the 2-thioether gives the cation **217**. Similar considerations apply to pyrazine-2-thione.[111]



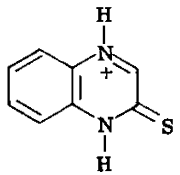
[*213*]



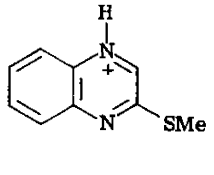
[*214*]



[*215*]



[*216*]



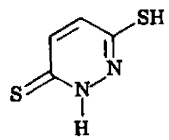
[*217*]

3,6-Dimercaptopyridazine exhibits an SH stretching band in the infrared region of the spectrum and, as might be expected by analogy with the corresponding dihydroxy compounds (see Section II,K), exists in the monothione–monomercapto form **218**,[119] this structure being confirmed by further infrared spectral comparisons.[120,271] The disulfide **219** has been formulated as shown on the basis of chemical evidence.[272]

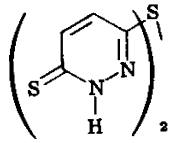
I. Triazinethiones

Infrared spectroscopy shows thioammeline to have structure **220**.[74]

[271] M. Kumagai, *Nippon Kagaku Zasshi* **81**, 1886 (1960).
[272] E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.* **81**, 6511 (1959).

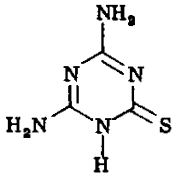


[*218*]

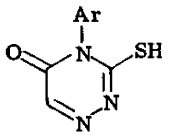


[*219*]

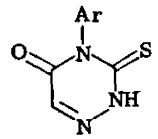
Although 1,2,4-triazinethiones have usually been formulated in the mercapto form, e.g. **221** (cf. reference 273), infrared and ultraviolet spectra appear to support the thione structure **222**.[274] However, on the basis of its infrared spectrum, **223** exists in the mercapto form,[275]



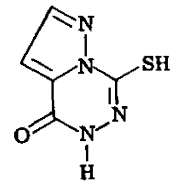
[*220*]



[*221*]



[*222*]



[*223*]

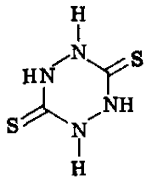
resembling 3-mercaptopyridazine-6-thione.

Infrared and proton resonance spectra indicate that the tetrazinedithione **223a** exists in the dithione form shown.[275a]

IV. Compounds with Potential Amino Groups

Amino groups are considerably less acidic than hydroxyl groups, and in aliphatic chemistry imino compounds are generally far less

[273] R. E. Hagenbach, E. Hodel, and H. Gysin, *Angew. Chem.* **66**, 359 (1954).
[274] M. Tišler and Ž. Vrbaški, *J. Org. Chem.* **25**, 770 (1960).
[275] C. Ainsworth, *J. Am. Chem. Soc.* **78**, 4475 (1956).
[275a] J. Sandström, *Acta Chem. Scand.* **15**, 1575 (1961).



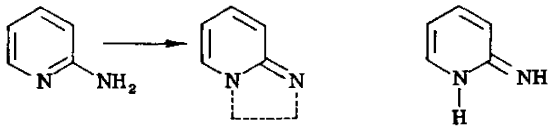
[223a]

stable than their carbonyl analogs.[276] Therefore, in the case of heterocyclic compounds, the amino forms might be expected to be relatively more favored than the corresponding hydroxy forms, and this is, indeed, the case.

A. Amino-pyridines and -benzpyridines

Much of the early work carried out to gain information concerning the tautomerism of these compounds employed chemical methods. 2-[277] and 4-Aminopyridine[278] can undergo alkylation both on the amino nitrogen and on the ring nitrogen atom; further, the ring closure reactions of 2-aminopyridine, i.e., conversion of **224** into **225**, were interpreted to indicate that it reacted in the imino form **226**.[279-281] The chemical properties of 2- and 4-aminopyridines and related compounds are different from those of aniline; for example, they are not easily diazotized and can sometimes be hydrolyzed with concomitant loss of ammonia. These facts have been taken to indicate that 2- and 4-aminopyridine, 2- and 4-aminoquinoline,[282] 9-aminophenanthridine,[283] and 9-aminoacridine[284] exist in the imino form. However, it gradually became apparent that these differences in chemical properties could be explained by the changed electronic environment of the groups concerned without recourse to tautomerism;

[276] For example, the equilibrium RCO·CH=CR·NHR ⇌ RCO·CH$_2$CR=NR appears to be very much in favor of the amino structure [cf. J. Weinstein and G. M. Wyman, *J. Org. Chem.* **23**, 1618 (1958)].
[277] A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber. deut. chem. Ges.* **54**, 814 (1921).
[278] A. E. Tschitschibabin, *Ber. deut. chem. Ges.* **58**, 1708 (1925).
[279] A. E. Tschitschibabin, *Ber. deut. chem. Ges.* **57**, 1168 (1924).
[280] A. E Tschitschibabin, *Ber. deut. chem. Ges.* **57**, 2092 (1924).
[281] A. E. Tschitschibabin, *Ber. deut. chem. Ges.* **58**, 1704 (1925).
[282] E. A. Steck and G. W. Ewing, *J. Am. Chem. Soc.* **70**, 3397 (1948).
[283] G. T. Morgan and L. P. Walls, *J. Chem. Soc.* p. 2225 (1932).
[284] R. R. Goodall and W. O. Kermack, *J. Chem. Soc.* p. 1546 (1936).



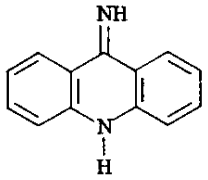
[224] [225] [226]

see, for example, the discussions by Albert and Goldacre[285] and by Angyal and Angyal.[286]

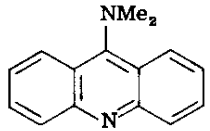
Further confusion arose from the incorrect interpretation of some of the early data obtained by physical methods. The dipole moment of 2-aminopyridine was reported to be temperature-dependent, and this was attributed to a change in the tautomeric character of the compound.[287] The high value of the dipole moment found for 4-aminopyridine was thought to preclude the existence of this substance in the imino form (**227**).[58] It was later pointed out that contributions from structure **228** might well lead to a high dipole moment for the imino form and that hydrogen bonding might be an important factor since different values were obtained in dioxane and in benzene.[288] The ultraviolet spectra of 2- and 4-amino-pyridine and -quinoline were interpreted in favor of an imino formulation,[282] and other investigators[45] also considered that 4-aminoquinoline existed in the imino form on the basis of the similarity of its ultraviolet spectrum with that of quinol-4-one. 9-Aminoacridine was originally reported to exist in the imino form **229** because its ultraviolet spectrum differed from that of the 9-dimethylamino derivative (**230**)[260,289]; however, it later became apparent that this difference was due to steric factors.

[227] [228]

[285] A. Albert and R. Goldacre, *Nature* **153**, 467 (1944).
[286] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.* p. 1461 (1952).
[287] C. A. Goethals, *Rec. trav. chim.* **54**, 299 (1935).
[288] L. N. Short, *J. Chem. Soc.* p. 4584 (1952).
[289] N. H. Turnbull, *J. Chem. Soc.* p. 441 (1945).

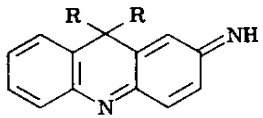


[229]



[230]

The chemical reactions of 3-aminopyridines, 3-aminoquinolines, etc. in which the amino group is *beta* to the hetero atom or is attached to a benzenoid ring are similar to those of aniline (cf. references 282, 290), and it has been generally accepted that these compounds exist overwhelmingly in the amino form. 2-Aminoacridine was not considered to exist as **231** (R = H), because **231** (R = Me) shows reac-



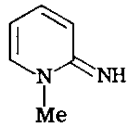
[231]

tions which are typical of an imine and are quite different from those of 2-aminoacridine[291]; however, 3- and 9-aminoacridine were thought to exist partly in the imino form.[292] Conclusive physical evidence has gradually accumulated supporting the amino formulation for the β- and benz-amino groups, and it has become clear during the last 10 years that α- and γ-amino compounds also exist predominantly in the amino form with very few exceptions.

In 1949, by comparison of the ultraviolet spectra of 2- and 4-aminopyridine with those of the alkylated forms of the alternative tautomers, Anderson and Seeger[293] showed that the parent compounds existed predominantly in the amino form and reported that the tautomeric composition did not vary greatly with the temperature. By using the pK method, in 1952 Angyal and Angyal[286] showed that

[290] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry." Methuen, London, 1960.
[291] A. Albert and R. Goldacre, *J. Chem. Soc.* p. 454 (1943).
[292] A. Albert and B. Ritchie, *J. Chem. Soc.* p. 458 (1943).
[293] L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.* **71**, 340 (1949).

the pK_T values for 2- and 4-aminopyridine and 4-aminoquinoline favored the amino forms and were 5.3, 3.3, and 3.2, respectively. Later that year two independent investigations demonstrated that the infrared spectra of all the aminopyridines and of 2- and 4-aminoquinoline contained bands characteristic of NH_2 groups, i.e., two ν N—H bands at ca. 3500 and 3400 cm^{-1}, and an NH_2 deformation band at ca. 1650 cm^{-1}, and that these bands are different from those associated with the $\diagdown$C=NH$\diagup$ group in 1-methylpyrid-2-onimine (**232**).[294,295] The infrared spectra of amino- and methylamino-pyridines and -quinolines show absorption bands that are charcteristic of monosubstituted-pyridine[296-298] or -quinoline[299] rings and of the amino group.[300] Changes in the infrared and ultraviolet spectra of amino-



[232]

pyridines and other compounds of this type, which occur after salt formation, have been correlated with the amino structure.[301]

Mason's infrared study[302] of the antisymmetrical and symmetrical NH-stretching frequencies which showed that aminopyridines and aminoazines existed predominantly as such has been extended to include a series of aminopolybenzpyridines[303] (Table VI). The intensities of the ν N—H bands increased with increasing "s" character of the NH bonds (cf. also reference 304) and varied over a 10^2 range, being the greatest for compounds in which there is strong conjugation between the amino nitrogen atom and the ring. Marked differences were

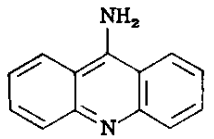
[294] C. L. Angyal and R. L. Werner, *J. Chem. Soc.* p. 2911 (1952).
[295] J. D. S. Goulden, *J. Chem. Soc.* p. 2939 (1952).
[296] A. R. Katritzky and A. R. Hands, *J. Chem. Soc.* p. 2202 (1958).
[297] A. R. Katritzky and J. N. Gardner, *J. Chem. Soc.* p. 2198 (1958).
[298] A. R. Katritzky, A. R. Hands, and R. A. Jones, *J. Chem. Soc.* p. 3165 (1958).
[299] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2942 (1960).
[300] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 3674 (1959).
[301] B. Witkop, *Experientia* **10**, 420 (1954).
[302] S. F. Mason, *J. Chem. Soc.* p. 3619 (1958).
[303] S. F. Mason, *J. Chem. Soc.* p. 1281 (1959).
[304] J. J. Elliot and S. F. Mason, *J. Chem. Soc.* p. 1275 (1959).

TABLE VI
COMPOUNDS SHOWN TO EXIST PREDOMINANTLY IN THE AMINO FORM BY INFRARED SPECTROSCOPY[a,b]

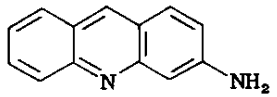
Ring system	Compounds of each type investigated (position of amino group indicated)
Pyridine	2-, 3-, 4-
Acridine	1-, 2-, 3-, 4-, 5-
Phenanthridine	6-, 9-, 2-(9-Me)
5,6-Benzoquinoline	4-, 2-(4-Me)
6,7-Benzoquinoline	3-, 4-
7,8-Benzoquinoline	4-, 6-, 1'-
1,2-Benzacridine	5-, 7-, 8-
2,3-Benzacridine	7-
3,4-Benzacridine	5-, 7-, 8-
Pyrimidine	2-, 4-, 5-, 2-(4,6-diMe)
Pyrazine	2-
Pyridazine	4-, 3-(6-Me)
1,2,4-Triazine	3-, 3-(5,6-diMe)

[a] S. F. Mason, *J. Chem. Soc.* p. 3619 (1958).
[b] S. F. Mason, *J. Chem. Soc.* p. 1281 (1959).

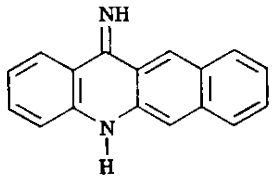
found between νNH_2 and ν=NH, the latter bands being weaker and occurring at frequencies 100–200 cm^{-1} lower. In particular it was found that the amino forms of **233** and **234** predominated, and pK_a data were reported which indicated K_T values of ca. 10 and 6000, respectively. However, the imino form of compound **235** is predominant.



[*233*]



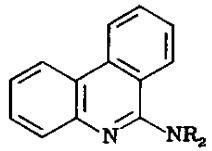
[*234*]



[*235*]

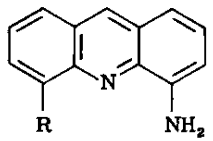
Ultraviolet spectral data, including the similarity between 9-aminoacridine and 9-aminoanthracene, led Craig and Short[305] to conclude that all the aminoacridines exist as such. The infrared solution spectra of the aminoacridines and aminoquinolines support the amino formulation[288]; similarly, infrared and ultraviolet spectral data have demonstrated that aminoisoquinolines also exist as such.[4]

The pK method was used to show that the value of pK_T for 9-aminophenanthridine (**236**, R=H) is 2.8, and ultraviolet spectral data are consistent with this conclusion when the fact that the dimethylamino derivative (**236**, R = Me) exhibits considerable steric hindrance to planarity is taken into consideration.[306]



[*236*]

The mono- and some di-aminoacridines,[289,305] 6- and 7-aminoquinoline,[307] and 3-aminopyridine[308] form monocations in which protonation occurs preferentially at the ring nitrogen atom. However, ultraviolet spectral data show that 1,9-diaminoacridine (**237**, R = NH_2) undergoes proton addition on the amino groups in preference to the cyclic nitrogen atom, whereas 1-amino-9-methylacridine (**237**, R = Me) is monoprotonated principally at the amino group in ethanol

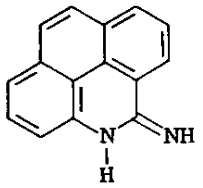


[*237*]

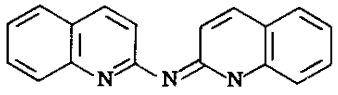
[305] D. P. Craig and L. N. Short, *J. Chem. Soc.* p. 419 (1945).
[306] C. B. Reese, *J. Chem. Soc.* p. 895 (1958).
[307] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.* p. 3329 (1951).
[308] A. Albert, *J. Chem. Soc.* p. 1020 (1960).

but at the ring nitrogen atom in aqueous solution.[309] Preferential protonation of the amino group in some of these cases has been attributed to the fact that the ring nitrogen atom is sterically hindered.

Medenwald[310] suggests that the infrared spectrum of aminoazapyrene (**238**) favors the imino form. Di-(2-quinolyl)amine has been reported[312] to exist in two modifications, one of which was the imino form **239**, but this seems improbable.



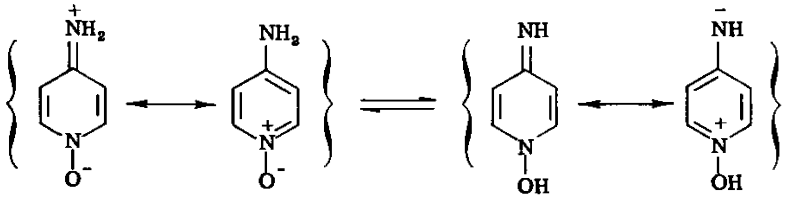
[238]



[239]

B. Aminopyridine 1-Oxides

Comparison by Gardner and Katritzky[91] of the pK_a values of the cations formed by 2- and 4-aminopyridine 1-oxide and the alkylated derivatives of both forms showed that in aqueous solution the amino form predominates for 2- and 4-aminopyridine 1-oxide (cf. **241** $\rightleftharpoons$ **242**) and the methylamino form for 2- and 4-methylaminopyridine 1-oxide by factors of ca. 10^9 and $>10^7$ in the 2- and 4-series, respectively. The ultraviolet spectra of the 4-isomer and its alkylated derivatives

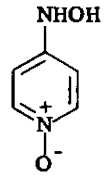


[240] [241] [242] [243]

[309] D. P. Craig, *J. Chem. Soc.* p. 534 (1946).
[310] H. Medenwald, *Chem. Ber.* **86**, 287 (1953).
[312] F. M. Hamer, *J. Chem. Soc.* **125**, 1348 (1924).

are too similar to allow differentiation, but ultraviolet spectral data do support this conclusion for the 2-isomer.[91,313] The infrared spectra of chloroform solutions of these compounds show bands corresponding to the amino or methylamino groups[91,300] and to the 2-[314] and 4-substituted pyridine 1-oxide rings.[315]

Earlier studies of 4-aminopyridine 1-oxide were less conclusive. The solid-state infrared spectrum could be interpreted to indicate the existence of both the imino structure and/or, more probably, the amino structure.[93] Comparison of the actual pK_a value of 4-aminopyridine 1-oxide with the value calculated using the Hammett equation was considered to indicate that the compound existed as such or as an equilibrium mixture with 1-hydroxypyrid-4-onimine, the latter possibility being considered the less likely on the basis of resonance and bond energies.[69] Resonance energy and ultraviolet spectral considerations have been advanced to support the 4-aminopyridine 1-oxide structure.[316] The presence of an infrared absorption band at

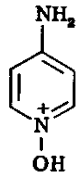


[244]

1250 cm^{-1}, the region in which ν N$^+$—O$^-$ would be expected to occur, has been reported as evidence that 4-hydroxylaminopyridine 1-oxide (**244**) exists as such.[317]

Aminopyridine 1-oxides are protonated on the oxygen atom to give mesomeric ions of type **245** as predicted theoretically[318] and confirmed by ultraviolet spectral comparisons (reference **91** and references therein).

[313] A. R. Katritzky, *J. Chem. Soc.* p. 191 (1957).
[314] A. R. Katritzky and A. R. Hands, *J. Chem. Soc.* p. 2195 (1958).
[315] A. R. Katritzky and J. N. Gardner, *J. Chem. Soc.* p. 2192 (1958).
[316] H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan* **73**, 140 (1953); *Chem. Abstr.* **47**, 4196 (1953).
[317] F. Parisi, P. Bovina, and A. Quilico, *Gazz. chim. ital.* **90**, 903 (1960).
[318] H. H. Jaffé, *J. Am. Chem. Soc.* **76**, 3527 (1954).

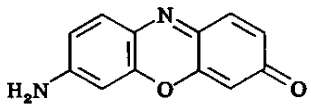


[245]

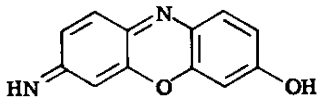
The fact that the equilibrium for aminopyridine 1-oxides is displaced further in favor of the amino form than is the equilibrium for aminopyridines is in accord with the mesomerism of these compounds. The stabilization of the amino forms (e.g., **241**) by structures of type **240** is more effective than the corresponding stabilization in the pyridine series since the negative charge is associated with the oxygen atom. The stabilization of the imino form (e.g., **242**) by structures of type **243** is less than in the pyridine series because of the adverse inductive effect of the oxygen atom.[91]

C. Amino Groups on Fused Benzene Rings

All the evidence suggests that such groups always exist in the amino form, and the reactions and behavior of these compounds resemble those of aniline and the naphthylamines. For example, the amino form of 7-aminophenazin-2-ones (**246**) would be expected to be more stable than the imino form (**247**), and their weak basicity supports this expectation.[318a]



[246]



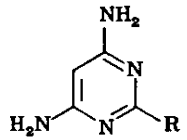
[247]

D. Aminopyrimidines

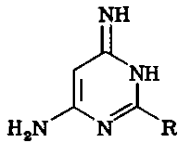
It was already suggested in the early investigations that the differences between the chemical properties of aminopyrimidines and anilines might result from tautomerism; see, for example, reference 319. The early infrared studies on the solid-state spectra of these

[318a] G. R. Ramage, E. H. Rodd, and J. K. Landquist, *in* "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVC, p. 1497. Elsevier, Amsterdam, 1960.
[319] J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.* p. 571 (1943).

compounds, although suggesting the amino formulation, were not unambiguous, and, too, the compounds studied were often complex structures.[129,130] Moreover, the early ultraviolet spectral investigation of compounds of type **248** (R = H, NH_2) was considered to prove that they existed in the imino form (**249**, R = H, NH_2), and in the case of **248** (R = NH_2) these findings were stated to be supported by



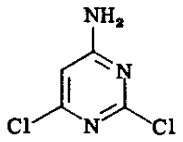
[248]



[249]

polarographic evidence although no details were reported.[320] At this time, other ultraviolet spectroscopic studies on pyrimidines were hampered by a lack of reference compounds.[134]

It gradually became apparent, however, that aminopyrimidines existed predominantly as such. An X-ray crystallographic investigation of the aminopyrimidines **250** and **251** showed that although the amino groups were hydrogen bonded to ring nitrogen atoms, these hydrogen bonds appeared to be asymmetrical and that the molecules exist in the amino forms.[321,322] Basicity measurements carried out on



[250]

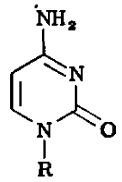
[251]

2- and 4-aminopyrimidine indicated that the amino forms were more stable than the imino forms in aqueous solution by factors of ca. 10^6.[323] The amino structure was further supported by the similarity of the ultraviolet spectra of these compounds and those of the 2- and

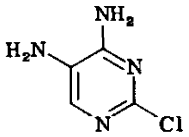
[320] L. F. Cavaliere and A. Bendich, *J. Am. Chem. Soc.* **72**, 2587 (1950).
[321] C. J. B. Clews and W. Cochran, *Acta Cryst.* **1**, 4 (1948).
[322] C. J. B. Clews and W. Cochran, *Acta Cryst.* **2**, 46 (1949).
[323] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.* p. 4035 (1955).

4-dimethylamino derivatives and by the fact that they were different from those of the corresponding 1-methyl-2- and -4-imino compounds (cf. also references 131, 137, and 324). Solid-state and nonaqueous solution infrared spectra of aminopyrimidines indicate that they exist largely in the amino form under these conditions since they show NH_2 stretching and deformation modes (cf. Table VI).[294,302] Recently, nuclear magnetic resonance spectroscopy has lent further support to the amino structure for 2-aminopyrimidine.[139]

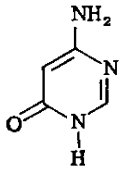
Cytidine (**252**, R = ribityl) has been shown to exist in the amino form,[325] and, using refined X-ray methods, the positions of all the hydrogen atoms in compound **253** were determined.[326] Structures **252** (R = Me) and **254** were shown to exist by ultraviolet spectral comparisons,[327] and structure **252** (R = Me) has been shown to predominate over **255** by a factor of ca. 10^5 by using the pK method.[327]



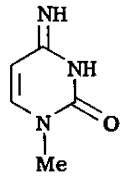
[*252*]



[*253*]



[*254*]



[*255*]

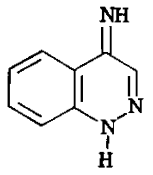
(For a discussion of tautomerism involving the carbonyl group of cytosine, see Section II,M.)

[324] V. I. Bliznyukov and V. A. Grin, *Trudy Khar'kov. Farm. Inst.* No. 1, p. 30 (1957); *Chem. Abstr.* **55**, 1632 (1961).
[325] S. Furberg, *Acta Cryst.* **3**, 325 (1950).
[326] N. E. White and C. J. B. Clews, *Acta Cryst.* **9**, 586 (1956).
[327] G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.* p. 855 (1955).

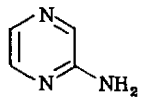
The ultraviolet spectrum of 4-aminoquinazoline has been interpreted to support the amino structure.[45]

E. Other Amino-diazines and -benzdiazines

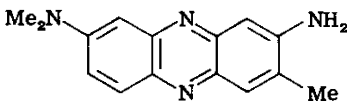
Amino-pyrazines and -pyridazines have been shown to exist predominantly in the amino form by infrared spectroscopic studies (cf. Table VI). Ultraviolet spectral data have been interpreted to indicate that 4-aminocinnoline exists predominantly in the imino form **256**,[45] but this conclusion, which was based on comparison of its spectrum with those of cinnolin-4-one and 4-ethoxycinnoline, is probably incorrect. Ultraviolet spectroscopic data strongly support the predominance of amino structures for 2-aminopyrazine (**257**)[111] and 2-aminoquinoxaline[183]; however, the former compound was at first erroneously concluded to exist in the imino form from ultraviolet spectral evidence.[328] Isolation of two isomers of 2-amino-8-dimethylamino-3-methylphenazine, assigned the amino and imino structures **258** and **259**, respectively, has been claimed,[329] but it is very unlikely that these assignments are correct.



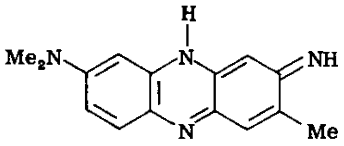
[*256*]



[*257*]



[*258*]



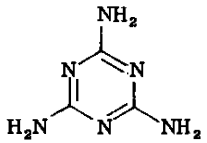
[*259*]

F. Aminotriazines

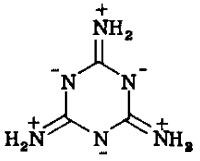
Melamine (**260**) has been studied extensively. Early X-ray crystal-

[328] Y. Pratt, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, p. 472. Wiley, New York, 1957.
[329] D. L. Vivian, *Nature* **188**, 746 (1960).

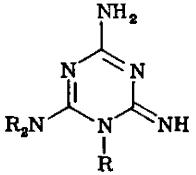
lographic studies indicated that it probably exists largely in the triamino form **260** (with contributions from canonical forms such as **261**) in the solid state,[330,331] although the actual positions of the hydrogen atoms were deduced from bond lengths, etc., and not determined directly. The triamino formulation of melamine, which was used to interpret its ultraviolet spectrum,[209,332] is strongly supported by the infrared spectrum.[333] Decisive evidence in support of the triamino formulation became available when K_T for the equilibrium between **260** and **262** (R = H) was found to be ca. 10^5 by measuring



[260]



[261]

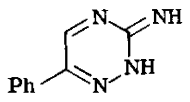


[262]

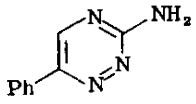
the pK of **262** (R = alkyl).[286,334] Molecular orbital calculations have been reported to favor the triamino structure rather than the triimino structure,[335] but the "mixed" structures, such as **262** (R = H), were not taken into consideration in these calculations.

In contrast to these findings, two independent reports have appeared in which the ultraviolet spectrum of 2-amino-1,3,5-triazine has been interpreted to indicate that this compound exists in the imino form,[336,337] but the correctness of these conclusions appears doubtful, especially since comparisons were not made with the spectra of the alkylated derivatives. Other investigators have interpreted the ultraviolet spectra of a series of amino- and diamino-1,3,5-triazines to indicate that the amino forms of these compounds predominate.[338]

[330] I. E. Knaggs, K. Lonsdale, R. G. Wood, and G. Williams, *Proc. Roy. Soc.* **A177**, 140 (1940).
[331] E. W. Hughes, *J. Am. Chem. Soc.* **63**, 1737 (1941).
[332] G. W. Costa, R. C. Hirt, and D. J. Salley, *J. Chem. Phys.* **18**, 434 (1950).
[333] W. J. Jones and W. J. Orville-Thomas, *Trans. Faraday Soc.* **55**, 203 (1959).
[334] J. R. Dudley, *J. Am. Chem. Soc.* **73**, 3007 (1951).
[335] M. J. S. Dewar and L. Paoloni, *Trans. Faraday Soc.* **53**, 261 (1957).
[336] C. Grundmann, L. Schwennicke, and E. Beyer, *Chem. Ber.* **87**, 19 (1954).
[337] A. Burger and E. D. Hornbaker, *J. Am. Chem. Soc.* **75**, 4579 (1953).
[338] R. C. Hirt and D. J. Salley, *J. Chem. Phys.* **21**, 1181 (1953).



[263]

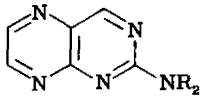


[264]

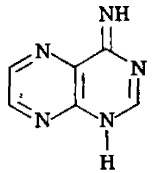
The infrared spectral method has been used to show that certain amino-1,2,4-triazines exist as such (Table VI). Although the separate isolation of **263** and **264** was claimed in 1940,[339] this report is probably erroneous.

G. Aminopteridines

The ultraviolet spectrum of 2-aminopteridine (**265**, R = H) is similar to that of its dimethylamino derivative (**265**, R = Me) suggesting that it exists in the amino form,[223] and similar evidence is available for 4- and 6-aminopteridine.[340] Basicity values show that the amino form of 4-aminopteridine is preferred to the imino form (**266**) by a factor of about 10^6.[341] 4-Aminopteridine is preferentially protonated at the 1-position.



[265]



[266]

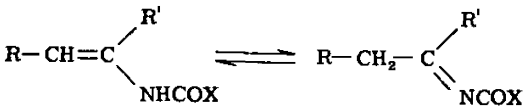
Brown and Jacobsen[341a] demonstrated by ultraviolet spectral comparisons that 2-amino-(3*H*)-pteridin-4-one was the predominant tautomeric form. The evidence in favor of 4-amino-(1*H*)-pteridin-2-one is less conclusive, but, nevertheless, convincing.

V. Compounds with Potential Substituted Amino Groups

The properties of a substituted aminoheterocyclic compound, "hetero ring"-NH—X, can be greatly influenced by the nature of the group

[339] J. B. Ekeley, R. E. Carlson, and A. R. Ronzio, *Rec. trav. chim.* **59**, 496 (1940).
[340] A. Albert, *Quart. Revs. (London)* **6**, 207 (1952).
[341] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.* p. 1978 (1960).
[341a] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.* p. 4413 (1961).

X. Alkyl groups usually have relatively little effect, and for convenience alkylamino compounds are included in the foregoing discussion of amino compounds. The acylamino (X = COR) and sulfonamido ($X = SO_2R$) derivatives are, however, treated separately. To some extent the tautomeric composition of these compounds can be predicted from a consideration of the properties of the analogous



[267] [268]

aliphatic and aromatic compounds, but there are inherent difficulties and these are discussed in the following section. The tautomeric equilibria **267** ⇌ **268** (X = OR, NH_2) in the closely related aliphatic series have been discussed on the basis of infrared spectral evidence.[342]

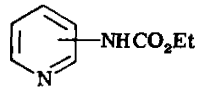
The ultraviolet spectra of many substituted aminopyridines were reported in 1959 with rather vague reference to their tautomerism[343]; however, the gross structure assigned to some of the sulfonamido compounds has been criticized.[344]

A. Acylamino-pyridines and -azines

2-, 3-, and 4-Acetamido- and -benzamido-pyridines have been shown to exist as such in aqueous solution by comparison of their ultraviolet spectra with those of both possible alkylated forms.[345] Basicity comparisons indicated that the acylamino form predominates in aqueous solution by factors of about 10^3, $>10^7$, and 10^5 in the 2-, 3-, and 4-series, respectively. The predominance of the acetamido and benzamido forms of the potentially tautomeric compounds is further supported by their infrared spectra which showed the bands characteristic of the 2-,[296] 3-,[298] and 4-substituted pyridine rings[297] and also the bands characteristic of the —NHCOMe or —NHCOPh

[342] M. Sato, *J. Org. Chem.* **26**, 770 (1961).
[343] P. Grammaticakis, *Bull. soc. chim. France*, p. 480 (1959).
[344] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* p. 378 (1961).
[345] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* p. 1317 (1959).

groups.[346] Infrared spectra also indicate that (ethoxycarbonylamino)-pyridines (**269**) exist as such.[347]



[269]

Sheĭnker and his collaborators[348] have studied the effect of replacing the hydrogen atoms of the acetamido group with halogen atoms on the tautomeric equilibrium of compounds of this type by using infrared and ultraviolet spectroscopy. Table VII summarizes

TABLE VII
Values of Log K_T = log (Imino/Amino) Calculated from Spectroscopic Data[a]

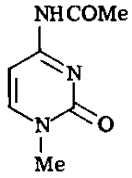
Ring system and substituent	Solid[b]	Solvent			
		H_2O	EtOH	Dioxane	C_6H_{14}
2-Substituted pyridine					
—$COCH_3$	A	—	—	—	—
—$COCHCl_2$	A	−1.9	−3.5	−3.8	—
—$COCCl_3$	A	−0.96	−2.2	−2.7	−4.5
—$COCF_3$	I	—	—	—	—
4-Substituted pyridine					
—$COCCl_3$	—	−1.5	−3.0	—	—
2-Substituted quinoline					
—$COCCl_3$	—	−0.5	−1.1	−1.4	−2.1
2-Substituted pyrimidine					
—$COCH_3$	A	—	—	—	—
—$COCHCl_2$	A	—	—	—	—
—$COCCl_3$	A	—	—	—	—

[a] Data taken from Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959).
[b] The A and I indicate the predominance of the amino and imino forms, respectively.

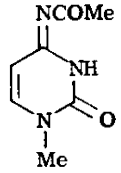
[346] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2067 (1959).
[347] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 676 (1960).
[348] Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959) [English translation: *Russ. J. Phys. Chem.* **33**, 303 (1959)].

their results. With increasing numbers of halogen atoms and increasing polarity of the solvent, the proportion of the imino form present at equilibrium increases.

Todd and his associates[327,349] have established that *N*-acetyl-1-methylcytosine exists predominantly as **270**, rather than as **271**, by



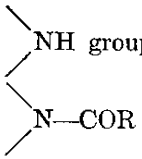
[*270*]



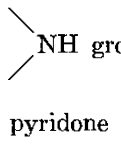
[*271*]

comparison of its ultraviolet spectrum with those of the alkylated derivatives of both forms. Other acetamidopyrimidinones which have been studied have also been assigned the acetamido structure.[137,350] The similarity of the ultraviolet spectra of 4-acetylaminoquinoline and its 6-nitro derivative to those of the methoxy analogs indicates that these compounds exist in the acetylamino form.[45]

In their acidity, basicity, and the directive influence exerted on electrophilic substitution reactions in benzenoid nuclei, acylamino groups show properties which are intermediate between those of free amino and hydroxyl groups, and, therefore, it is at first surprising to find that the tautomeric behavior of acylaminopyridines closely resembles that of the aminopyridines instead of being intermediate between that of the amino- and hydroxy-pyridines. The basicities of the acylaminopyridines are, indeed, closer to those of the methoxypyridines than to those of the aminopyridines, the position of the tautomeric equilibrium being determined by the fact that the acyliminopyridones are strong bases like the iminopyridones and unlike the pyridones themselves. Thus, relative to the conversion of an



NH group into an oxo group, converting an

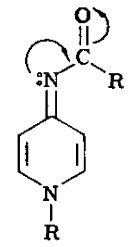


NH group into an

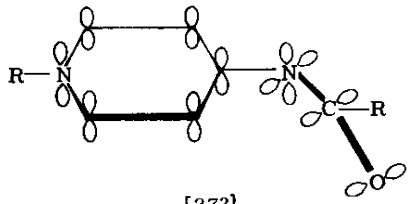
N—COR group decreases the basicity of a pyridone form much

[340] D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.* p. 2384 (1956).
[350] W. Pfleiderer and G. Strauss, *Ann. Chem. Liebigs* **612**, 173 (1958).

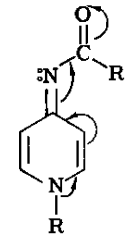
less than that of a pyridine form. It appears that there must be some specific destabilization of the acyliminopyridones relative to the acylaminopyridines. This probably[345] results from the fact that mesomerism of type **272** (which requires the C=O π-orbital to be in the plane of the ring, cf. **273**) and mesomerism of type **274** (which requires the C=O π-orbital to be perpendicular to the ring, cf. **275**) cannot occur simultaneously, whereas simultaneous overlap of the nitrogen spare electron pair both with the ring (**276**) and with the carbonyl π-orbitals (**277**) is possible (cf. **278**).



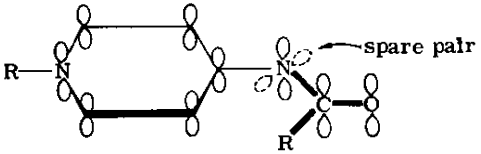
[*272*]



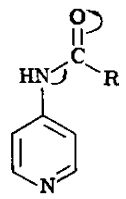
[*273*]



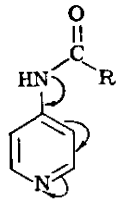
[*274*]



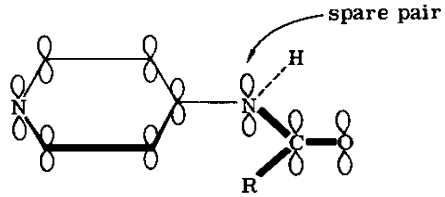
[*275*]



[*276*]



[*277*]



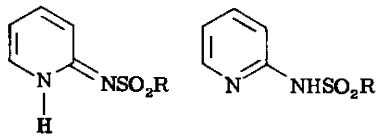
[*278*]

B. Acylaminopyridine 1-Oxides

The infrared spectra of 2-, 3-, and 4-acetamido- and 2- and 3-benzamido-pyridine 1-oxides show bands characteristic of the 2-, 3-, or 4-substituted pyridine 1-oxide ring[261,314] and of the $—NHCOCH_3$ or $—NHCOC_6H_5$ group,[346] indicating that these compounds exist predominantly in the acylamino form, as would be expected.

C. Sulfonamido Compounds

Mesomerism involving sulfonyl groups is relatively weak, and in the case of the sulfonyliminopyridones (**279**) destabilization caused by the factors previously mentioned for the acyliminopyridones should be less important. Early ultraviolet spectral comparisons showed that acetylsulfapyridine[351,352] and sulfapyridine[353] (cf. reference 354) exist in aqueous solution as mixtures of comparable amounts of **279** and **280**. A recent investigation of 2-, 3-, and 4-methanesulfonamido-



[279] [280]

pyridine, using infrared and ultraviolet spectroscopy and the basicity method, led to the conclusion that the ratios of the imino (cf. **279**) or zwitterion forms to the amino forms in aqueous solution were approximately 10, 0.1, and 30 for the 2-, 3-, and 4-series, respectively.[344] Russian investigators[355] concluded from ultraviolet and infrared spectral data that 2-(*p*-aminobenzenesulfonamido)-pyridine and -pyrimidine exist in the imido form in the solid state and that the imido form also predominates in aqueous solution, the proportion of the amino form increasing in ethanol and becoming predominant in dioxane. Extension of this investigation to include several related

[351] R. G. Shepherd, A. C. Bratton, and K. C. Blanchard, *J. Am. Chem. Soc.* **64**, 2532 (1942).
[352] J. M. Vandenbelt and L. Doub, *J. Am. Chem. Soc.* **66**, 1633 (1944).
[353] S. J. Angyal and W. K. Warburton, *Australian J. Sci. Research* **4**, 93 (1951).
[354] Yu. N. Sheĭnker, I. Ya. Postovskiĭ, N. M. Voronina, and V. V. Kushkin, *Zhur. Fiz. Khim.* **31**, 1745 (1957); *Chem. Abstr.* **52**, 5971 (1958).
[355] Yu. N. Sheĭnker and I. K. Kuznetsova, *Zhur. Fiz. Khim.* **31**, 2656 (1957).

systems led to similar conclusions[348] (Table VIII). The tautomerism of compounds of this type has been reviewed.[356]

Table VIII
Values of Log K_T = Log (Imino/Amino) Calculated from Spectroscopic Data[a]

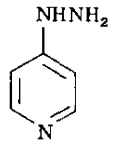
Ring system and substituent	Solid[b]	Solvent			
		H_2O	EtOH	Dioxane	C_6H_{14}
2-Substituted pyridine					
$—SO_2CH_3$	—	0.8	−0.6	−1.7	−2.1
$—SO_2C_6H_5$	I	1.8	−0.05	−1.4	−2.0
$—SO_2C_6H_4NH_2$	—	0.9	−0.6	−1.9	—
4-Substituted pyridine					
$—SO_2C_6H_5$	—	2.7	0.1	−0.4	—
2-Substituted pyrimidine					
$—SO_2C_6H_5$	I	—	—	—	—
2-Substituted quinoline					
$—SO_2C_6H_5$	—	large	1.2	0.3	—

[a] Data taken from Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959).
[b] The I denotes the predominance of the imino form.

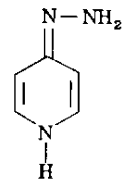
D. Hydrazino Compounds

The possible tautomerism of 2-hydrazinoquinoline was discussed by Marckwald and Meyer in 1900.[90] 4-Hydrazinopyridine is considered to exist as such (**281**) rather than in the alternative hydrazone form (**282**) by analogy with 4-aminopyridine and on the basis of its chemical reactivity.[357,358] Available pK_a data[359] indicate that K_T may be of the order of 10^3. 1,2-Bis(1-isoquinolyl)hydrazine, unlike the corresponding 2-pyridyl and 2-quinolyl compounds, was formulated as **283** because of its color.[360] The 1,2-bis(pyrimidyl)hydrazines, however,

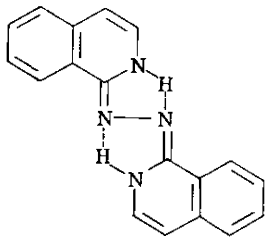
[356] H. Dorn, G. Hilgetag, and A. Rieche, *Angew. Chem.* **73**, 560 (1961).
[357] S. Hünig, H. Balli, K. H. Fritsch, H. Herrmann, G. Köbrich, H. Werner, E. Grigat, F. Müller, H. Nöther, and K.-H. Oette, *Angew. Chem.* **70**, 215 (1958).
[358] S. Hünig and H. Werner, *Ann. Chem. Liebigs* **628**, 46 (1959).
[359] S. Hünig and H. Balli, *Ann. Chem. Liebigs* **628**, 56 (1959).
[360] T. Kauffmann, H. Hacker, and C. Kosel, *Z. Naturforsch.* **14b**, 602 (1959).



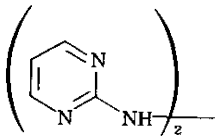
[281]



[282]



[283]

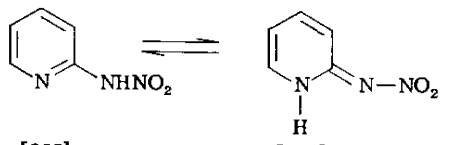


[284]

have been assigned structures of type **284** on the basis of their infrared spectra.[361]

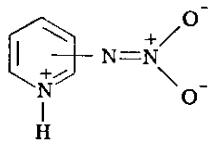
E. Nitramido Compounds

The alkylation of 2-nitramidopyridine (**285** ⇌ **286**) with dimethyl sulfate yields only the 1-methyl derivative[362]; however, both possible derivatives were obtained for some substituted compounds,[363,364] and this behavior was thought to be associated with their tautomerism. Diazomethane also gave a mixture of alkylated products.[365] Infrared



[285]

[286]

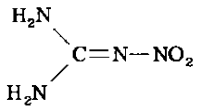


[287]

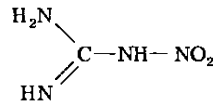
[361] A. Kreutzberger, *Z. physik. Chem. (Frankfurt)* **24**, 368 (1960).
[362] A. E. Tschitschibabin and G. P. Menschikow, *Ber. deut. chem. Ges.* **58**, 406 (1925).
[363] A. E. Tschitschibabin and A. W. Kirssanow, *Ber. deut. chem. Ges.* **61**, 1223 (1928).
[364] A. E. Tschitschibabin and A. W. Kirssanow, *Ber. deut. chem. Ges.* **61**, 1236 (1928).
[365] A. Taurins and S. J. Viron, *Can. J. Chem.* **31**, 1048 (1953).

spectral data led to the conclusion that the solid 2-, 3-, and 4-nitramidopyridines all exist as zwitterions (**287**).[366] In the case of 2-nitramidopyridine, this conclusion was confirmed and extended by Russian workers,[348] who interpreted its infrared spectrum to show that it exists in the imino form in the solid state. By using ultraviolet spectroscopy, they further showed that the imino form predominates by a small factor ($pK_T = 0.2$) in ethanol but that the proportion of the amino form increases in dioxane ($pK_T = -0.8$).[348]

It is interesting to note that the acyclic analog, nitroguanidine, exists in the symmetrical form **288** rather than as **289**. Structure **288** has been established by ultraviolet and proton nuclear magnetic resonance spectroscopy, X-ray crystallography, dipole moments, and pK measurements (see reference **367** and references therein).



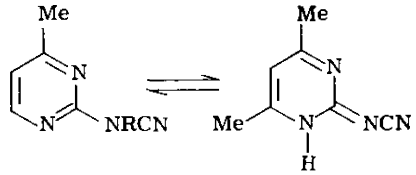
[288]



[289]

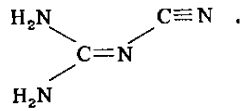
F. Cyanamido Compounds

The ultraviolet spectrum of the tautomeric compound **290** (R = H) ⇌ **291** is qualitatively similar, but quantitatively dissimilar, from that of the methyl derivative (**290**, R = Me),[368] and it may be tentatively concluded that both forms **290** (R = H) and **291** are present



[290]

[291]



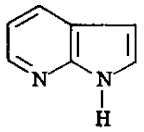
[292]

in the equilibrium mixture. As an example from aliphatic chemistry, Jones and Orville-Thomas[369] have used infrared spectral data to show that dicyandiamide exists in the diamino form (**292**).

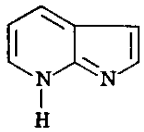
[366] A. Taurins, *Can. J. Chem.* **36**, 465 (1958).
[367] R. E. Richards and R. W. Yorke, *Trans. Faraday Soc.* **54**, 321 (1958).
[368] L. Fabbrini, *Gazz. chim. ital.* **87**, 1293 (1957).
[369] W. J. Jones and W. J. Orville-Thomas, *Trans. Faraday Soc.* **55**, 193 (1959).

G. Amino Group as Part of a Fused Heterocyclic Ring

The tautomerism of diazaindenes has been mentioned by Campbell,[370] and ultraviolet spectral data indicate that structure **293** is preferred to **294**.

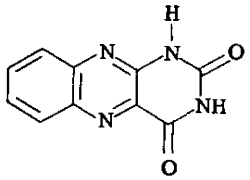


[293]



[294]

Alloxazines (**295**) have been considered to exist as such, and not as isoalloxazines (**296**, R = H), because their ultraviolet spectra and



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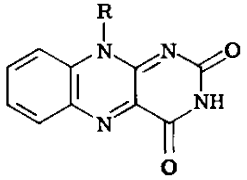


[296]

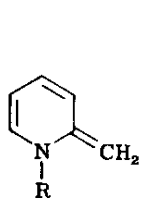
physical and chemical properties are different from those of the 9-alkylisoalloxazines **296** (R = alkyl).[371] This investigation was carried out in 1934, however, and could advantageously be repeated using modern techniques.

VI. Potential Methyl or Substituted Methyl Compounds

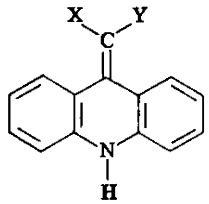
In comparison with mercapto-, hydroxy-, and amino-pyridines, methylpyridines should show an even greater tendency to exist in the methyl form [instead of as pyridmethines (**297**)] than do the amino compounds to exist as such. If the methyl carbon atom carries an electron-withdrawing group, it might be expected that structures of type **297** would be stabilized. Fused benzo groups should also tend to stabilize the methine form, and tautomerism involving **298** has, indeed, been discussed for acridine derivatives. However, other, more stable, tautomeric possibilities sometimes occur (see following).

[370] N. Campbell, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, p. 1033. Elsevier, Amsterdam, 1959.

[371] K. G. Stern and E. R. Holiday, *Ber. deut. chem. Ges.* **67**, 1442 (1934).

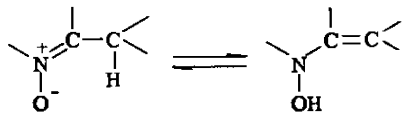


[297]



[298]

The interesting tautomeric equilibrium **299** ⇌ **300** has not yet been reported for heterocyclic *N*-oxides, although it has been described for acyclic compounds.[372]



[299] [300]

A. Methylpyridines

Chemical arguments based on ring closure reactions, etc., were advanced for the existence of 2-methylpyridine as **297** (R = H),[373] but it was soon recognized that the methyl form is greatly predominant.[374] Thus, pyridmethines, such as **297** (R = Me), are strong bases giving an alkaline solution in water,[375] and pK_a considerations indicate that the K_T values are probably $\geqslant 10^6$. The infrared spectra of the methylpyridines[296-298,376] show that they are true pyridines, and this finding is supported by their ultraviolet spectra.[377] Elvidge and Jackman[378] have recently shown by nuclear magnetic resonance spec-

[372] J. Thesing and G. Michel, *Angew. Chem.* **67**, 516 (1955).

[373] A. E. Tschitschibabin, *Ber. deut. chem. Ges.* **60**, 1607 (1927).

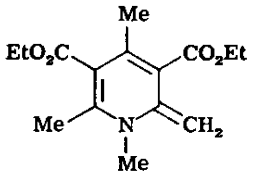
[374] C. H. Cartwright and J. Errera, *Compt. rend. acad. sci.* **200**, 914 (1935).

[375] O. Mumm, *Ann. Chem. Liebigs* **443**, 272 (1925).

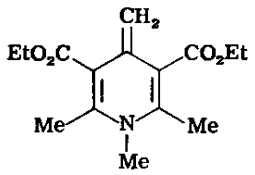
[376] D. A. Long, F. S. Murfin, J. L. Hales, and W. Kynaston, *Trans. Faraday Soc.* **53**, 1171 (1957).

[377] L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.* **71**, 343 (1949).

[378] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* p. 859 (1961).



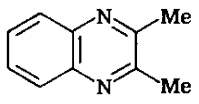
[301]



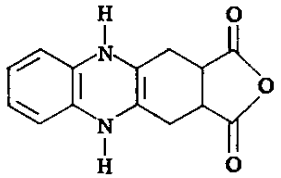
[302]

troscopy that the 2-methylene compound (**301**) is the predominant tautomer in the equilibrium **301** $\rightleftharpoons$ **302**.

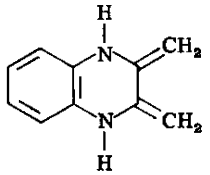
2,3-Dimethylquinoxaline (**303**) has been reported to undergo a Diels-Alder reaction with maleic anhydride to give **304**, **305** having been postulated to be the reactive form.[379] However, attempted confirmation of this unexpected result has shown that **304** is not the correct structure of the reaction product.[379a] In 1931, other chemical evidence was advanced in support of structure **305**,[380] but it would no longer be considered valid.



[303]



[304]



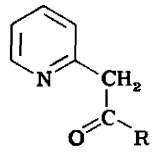
[305]

B. Acylmethyl Derivatives

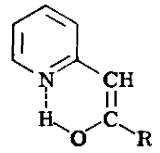
Three types of tautomeric structures must be considered for acyl-

[379] A. Schönberg and A. Mostafa, *J. Chem. Soc.* p. 654 (1943).
[379a] Personal communication from Dr. G. W. H. Cheeseman (1962).
[380] R. A. Ogg and F. W. Bergstrom, *J. Am. Chem. Soc.* **53**, 1846 (1931).

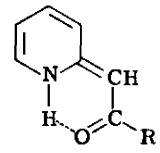
methyl compounds; for example, 2-acylmethylpyridines can exist as **306**, **307**, and **308**. The stronger the hydrogen bond, the greater will be the similarity between structures of types **307** and **308**. Infrared spectroscopy has been used to demonstrate that structures of type **307** are the stable forms of 2-phenacylpyridine (**307**, R = Ph)[381] and the α-naphthoyl analog,[382] and this conclusion is supported by ultraviolet spectral data and chemical evidence.[383] Similar examples are known in the pyrazine series.[384]



[306]

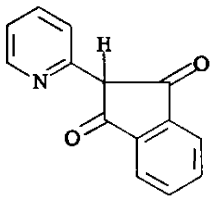


[307]

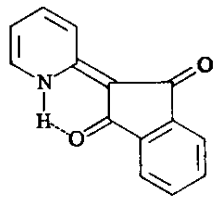


[308]

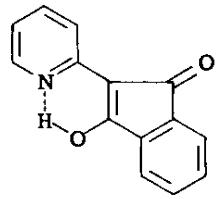
The analogous structures **309**, **310**, and **311** have been suggested for the pyrophthalones. Early work favored structure **309** (see reference 385 and references therein). Later, ultraviolet spectral data showed the presence of an extended conjugated system, and comparison with the spectra of the *N*-methyl compounds suggested structure **310**.[385]



[309]

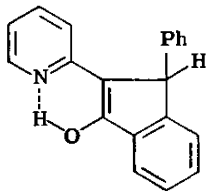


[310]



[311]

[381] R. F. Branch, *Nature* **177**, 671 (1956).
[382] R. F. Branch, *Nature* **179**, 42 (1957).
[383] A. H. Beckett, K. A. Kerridge, P. M. Clark, W. G. Smith, *J. Pharm. and Pharmacol.* **7**, 717 (1955).
[384] N. Naqvi, E. L. Amma, Q. Fernando, and R. Levine, *J. Phys. Chem.* **65**, 218 (1961).
[385] E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.* **37**, 563 (1959).

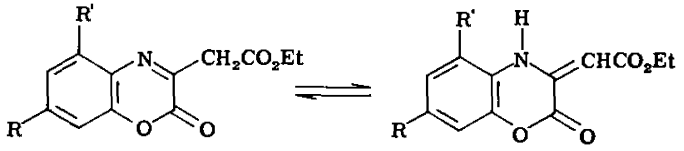


[312]

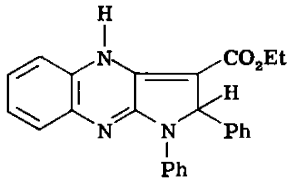
However, the infrared spectra of the pyrophthalones were interpreted in favor of structure **311**.[386] The related compound **312** has been formulated as shown.[386]

C. Ethoxycarbonylmethyl Derivatives

Infrared spectroscopy indicates that equilibria of type **313** ⇌ **314** (R = Me, R′ = Ac and R = Ac, R′ = Me) favor structure **314** in the solid state[387]; for similar work on 1,4-oxazin-2-one derivatives, see references 388 and 388a. Structure **315** has also been suggested on the basis of infrared evidence.[389]



[313] [314]

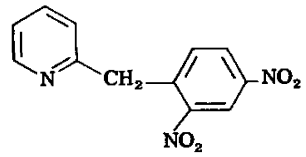


[315]

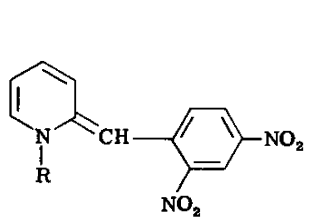
[386] D. G. Manly, A. Richardson, A. M. Stock, C. H. Tilford, and E. D. Amstutz, *J. Org. Chem.* **23**, 373 (1958).
[387] A. Butenandt, E. Biekert, M. Däuble, and K. H. Köhrmann, *Chem. Ber.* **92**, 2172 (1959).
[388] E. Biekert and L. Enslein, *Chem. Ber.* **94**, 1851 (1961).
[388a] E. Biekert, D. Hoffmann, and L. Enslein, *Chem. Ber.* **94**, 2778 (1961).
[389] W. R. Vaughan and R. C. Tripp, *J. Am. Chem. Soc.* **82**, 4370 (1960).

D. Benzyl-pyridines and -azines

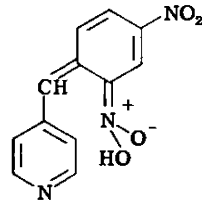
2-(2,4-Dinitrobenzyl)pyridine (**316**) exhibits phototropy, turning blue in light, and, since the color resembles that of the methide (**317**, R = Me), tautomerism to **317** (R = H) has been postulated to occur during the phototropy.[390] Ultraviolet spectral data led Clark and Lothian[391] to suggest that the coloring process consists of the transfer of a proton during the bending vibration of the CH_2—C=N group in the electronically excited molecule, and Gutowsky and Rutledge[392] have reported that the blue color is not due to a triplet state. The color change, which also takes place in solution, causes changes in the infrared spectrum.[393] The isomeric 4-(2,4-dinitrobenzyl)pyridine also shows photochromotropic properties in solution, but not in the solid state; these color changes possibly involve forms of type **318**.[394]



[316]



[317]

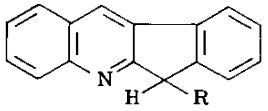


[318]

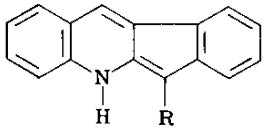
The indenoquinoline **319** (R = H) exists as such, but ultraviolet spectral data indicate that the presence of electron-withdrawing

[390] A. E. Tschitschibabin, B. M. Kuindshi, and S. W. Benewolenskaja, *Ber. deut. chem. Ges.* **58**, 1580 (1925).
[391] W. C. Clark and G. F. Lothian, *Trans. Faraday Soc.* **54**, 1790 (1958).
[392] H. S. Gutowsky and R. L. Rutledge, *J. Chem. Phys.* **29**, 1183 (1958).
[393] R. Hardwick, H. S. Mosher, and P. Passailaigue, *Trans. Faraday Soc.* **56**, 44 (1960).
[394] H. S. Mosher, C. Souers, and R. Hardwick, *J. Chem. Phys.* **32**, 1888 (1960).

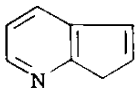
groups causes the tautomeric form **320** (R = CN or CHO) to predominate.[395] The equilibrium **321** ⇌ **322** has been reported.[396]



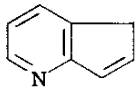
[*319*]



[*320*]

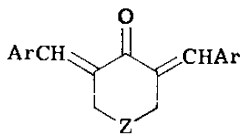


[*321*]

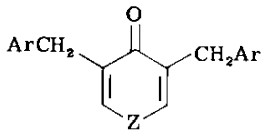


[*322*]

A different type of tautomeric relationship exists between compounds of types **323** and **324**. Both types of structure can be isolated, pyridones (**324**, Z = N—Me)[397] and pyrones (**324**, Z = O)[398] being formed when **323** (Z = N—Me or O) is heated with palladium on charcoal in ethylene glycol. Similar isomerizations in the quinol-4-one series have been reported.[399]



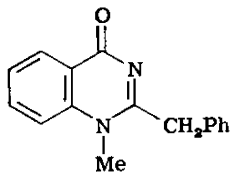
[*323*]



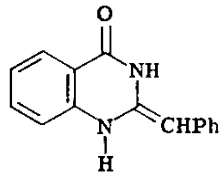
[*324*]

The alkaloid aborine has been shown to exist as **324a**[399a] although earlier the form **324b** had been assigned.

[395] W. Treibs, W. Schroth, H. Lichtmann, and G. Fischer, *Ann. Chem. Liebigs* **642**, 97 (1961).
[396] M. M. Robison, 134th Meeting, Am. Chem. Soc. Abstr. p. 16P (September 1958, Chicago).
[397] N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.* **77**, 1852 (1955).
[398] N. J. Leonard and D. Choudhury, *J. Am. Chem. Soc.* **79**, 156 (1957).
[399] P. I. Ittyerah and F. G. Mann, *J. Chem. Soc.* p. 467 (1958).
[399a] D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta, and H. K. Miller, *Tetrahedron* **16**, 224 (1961).



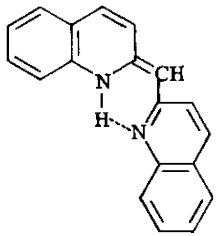
[*324a*]



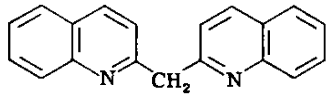
[*324b*]

E. Di- and Tri-quinolylmethanes

Di(2-quinolyl)methane can be obtained in a red and in a colorless modification, and chemical evidence suggests that these correspond to structures **325** and **326**, respectively.[311,400] These structural assignments are confirmed by ultraviolet spectral comparisons, which also show that an equilibrium mixture containing about 25% of **326** is formed in solution at a measurable rate.[400] Scheibe and Riess[400] have suggested that the hydrogen bond in **325** may be symmetrical. The tautomerism of tri(2-quinolyl)methane is similar to that of the di(2-quinolyl) analog.[400] The corresponding di(phenanthridyl) and di(benzoquinolyl) compounds have been reported.[401] Metallic complexes of these compounds have a structure similar to **326**, their relative stability being related to the stability of the NH isomers.[402]



[*325*]



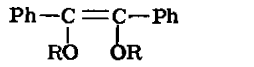
[*326*]

F. Acyloins

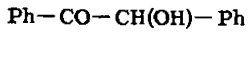
Although esters and ethers (**327**, R = alkyl or acyl) of the enediol form (**327**, R = H) of benzoin are known, the parent compound exists

[400] G. Scheibe and W. Riess, *Chem. Ber.* **92**, 2189 (1959).
[401] G. Scheibe and H. J. Friedrich, *Chem. Ber.* **94**, 1336 (1961).
[402] G. Scheibe, H. J. Friedrich, W. Gückel, and H. H. Credner, *Angew. Chem.* **73**, 273 (1961).

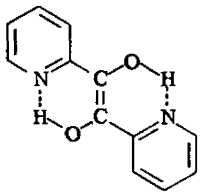
in the keto form **328**. However, the enediol structure of α-pyridoin-type compounds can be stabilized by hydrogen bonding, and, indeed, the absence of a C=O band and the broad OH peak in the infrared spectrum,[403,404] the low dipole moment,[403] and ultraviolet spectral evidence[405] show clearly that α-pyridoin exists as **329**. The structural similarity between **329** and **307** is apparent. The chemical properties of α-pyridoin also strongly support the enediol formulation.[405–408] On the basis of chemical evidence, enediol structures have been assigned to the analogous products from quinoline-2-aldehyde[409] and quinoline-2-aldehyde 1-oxide[410]; this assignment is further supported for the former compound by infrared spectral data. The mixed condensation products **330**[411] and **331**[412] also exist as enediols, although **330** is



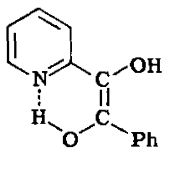
[*327*]



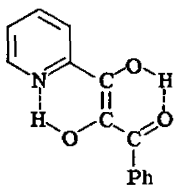
[*328*]



[*329*]



[*330*]



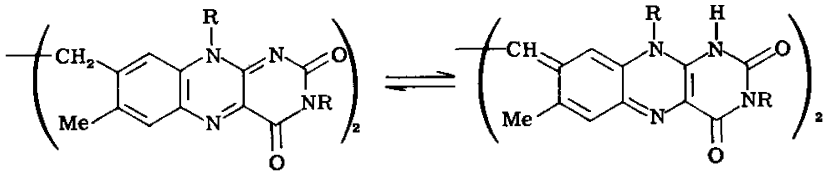
[*331*]

rather unstable, being only monochelated.

[403] W. Lüttke and H. Marsen, *Z. Elektrochem.* **57**, 680 (1953).
[404] H. R. Hensel, *Angew. Chem.* **65**, 491 (1953)
[405] B. Eistert and H. Munder, *Chem. Ber.* **88**, 215 (1955).
[406] B. Eistert, *Bull. soc. chim. France* **22**, 288 (1955).
[407] W. Mathes, W. Sauermilch, and T. Klein, *Chem. Ber.* **84**, 452 (1951).
[408] F. Cramer and W. Krum, *Chem. Ber.* **86**, 1586 (1953).
[409] C. A. Buehler and J. O. Harris, *J. Am. Chem. Soc.* **72**, 5015 (1950).
[410] C. A. Buehler, L. A. Walker, and P. Garcia, *J. Org. Chem.* **26**, 1410 (1961).
[411] C. A. Buehler, J. W. Addleburg, and D. M. Glen, *J. Org. Chem.* **20**, 1350 (1955).
[412] B. Eistert and H. Munder, *Chem. Ber.* **91**, 1415 (1958).

G. Flavins

Tautomerism of type **332** ⇌ **333** has been postulated for the flavins.[413]



[*332*] [*333*]

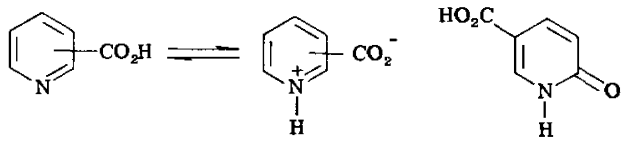
VII. Pyridinecarboxylic Acids

The ultraviolet spectra of the pyridinecarboxylic acids (**334**) were initially interpreted assuming that the proportion of the zwitterion structure **335** was not appreciable,[414,415] and the early pK work was inconclusive.[416] However, Jaffé's calculations based on the Hammett equation indicated that about 95% of nicotinic and isonicotinic acids existed in the zwitterion form,[69] and ultraviolet spectral data showed that the actual percentages of picolinic, nicotinic, and isonicotinic acids existing in the zwitterion form in aqueous solution are **94**, **91**, and 96%, respectively.[417] This was later confirmed by Stephenson and Sponer,[418] who further demonstrated that the proportion of the zwitterion form decreases in solvents of low dielectric constant, becoming very low in ethanol. Dipole moment data indicate that isonicotinic acid exists as such in dioxane,[418] and 6-hydroxypyridine-3-carboxylic acid has been shown to exist in form **336** using pK data.[308]

VIII. Pyridine Aldehydes

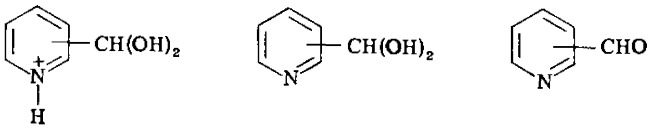
Ultraviolet spectra show that pyridine-2-, -3-, and -4-aldehydes exist as hydrated cations (**337**) in aqueous solution at low pH values.

[413] P. Hammerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta* **42**, 2164 (1959).
[414] H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.* **58**, 548 (1954).
[415] E. B. Hughes, H. H. G. Jellinek, and B. A. Ambrose, *J. Phys. Colloid Chem.* **53**, 414 (1949).
[416] R. F. Evans, E. F. G. Herington, and W. Kynaston, *Trans. Faraday Soc.* **49**, 1284 (1953).
[417] R. W. Green and H. K. Tong, *J. Am. Chem. Soc.* **78**, 4896 (1956).
[418] H. P. Stephenson and H. Sponer, *J. Am. Chem. Soc.* **79**, 2050 (1957).

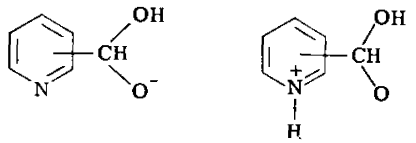


[334] [335] [336]

These cations have pK_1 values of about 4–5 and pK_2 values of about 12–13. At near-neutral pH values, the ultraviolet spectra indicate that two species are present in about equal quantity, one being more highly conjugated than the other.[75] The obvious explanation of these results is that the pyridinium proton in **337** ionizes at pH 4–5 to give an equilibrium mixture of **338** and **339** and that, above pH 12–13, **340** is formed. For reasons which are neither clear nor convincing, the original investigators[75] rejected this explanation in favor of an equilibrium containing ca. 50% of **339** and **341**. The same workers have also studied the tautomerism of 3-methoxypyridine-2- and -4-aldehyde and reached similar conclusions,[419] which appear to be open to question. (The pyridoxal analogs are discussed in Section II,E.)



[337] [338] [339]



[340] [341]

IX. Pyridine Aldoximes

The tautomerism of heteroaromatic aldoximes between forms of types **342** and **343** has been investigated by the basicity method and

[419] K. Nakamoto and A. E. Martell, *J. Am. Chem. Soc.* **81**, 5863 (1959).

by ultraviolet spectroscopy.[420] The results obtained in aqueous solution and summarized in Table IX indicate that the aldoxime forms

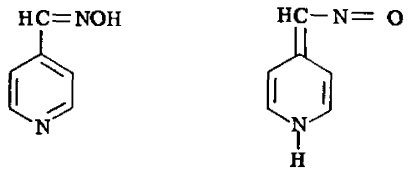
TABLE IX

TAUTOMERIC EQUILIBRIUM CONSTANTS (K_T = [NH FORM]/[OH FORM])[a]

Compound	pK_T	
	Basicity method	Spectroscopic method
Pyridine-2-aldoxime	−4.4	−4.1
Pyridine-3-aldoxime	−5.1	—
Pyridine-4-aldoxime	−3.8	−3.8
Quinoline-2-aldoxime	−3.8	—

[a] S. F. Mason, *J. Chem. Soc.* p. 22 (1960).

(**342**) are favored by factors of about 10^4–10^5. Ultraviolet and infrared spectral data indicate an even greater preference for forms of type **342** in ethanol and carbon tetrachloride, respectively. The large difference between this behavior and that of hydroxypyridines, where the proton also moves between an OH group and a cyclic nitrogen atom, has been ascribed to the weakness of the interaction between the nucleus and the oximino portion of the molecule.



[342] [343]

[420] S. F. Mason, *J. Chem. Soc.* p. 22 (1960).

Author Index

Numbers in parentheses are footnote numbers and are inserted to enable the reader to locate a reference when the authors' names do not appear in the text.

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Subject Index

A

J

K

L

M

N

O

P

Q

U

V

X